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Abu Al Qasim Al Zahrawi

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Dose reduction in patients with pre-existing mild to moderate renal impairment. In patients requiring repeated administration of Zometa, serum creatinine should be evaluated prior to each dose. If renal function has deteriorated, the dose should be withheld. Limited clinical data in patients with severe hepatic insufficiency; no specific recommendations can be given for this patient population. Overhydration should be avoided in patients at risk of cardiac failure. Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving bisphosphonates, including Zometa. The majority of these cases has been associated with dental procedures. Therefore, patient should inform the dentist while under dental treatment or if dental surgery is foreseen. Patients treated with Zometa (zoledronic acid) should not be treated with Aclasta. 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Reference: 1. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer Clin Oncol. 2003;21:4042-4057. 2. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skele complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer. 2003;98:1735-1744.

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SYMPOSIA

Medical & Surgical Aspects of Neuroendocrine Disorders
03-04 April 2007/15–16 Rabia Al Awal 1428

ART & Perinatology Hand-in-Hand for a Healthy Generation
24-25 April 2007/07-08 Rabia Al Thani 1428
(Workshop by Dept.: 26 April 2007/09 Rabia Al Thani 1428)

King Faisal Heart Institute 2nd International Symposium "Cardiac Diseases: Challenges of the Future"
22-24 May 2007/05-07Jumada Al Awal 1428

OrthoKids International Symposium
06-07 November 2007/25-26 Shawwal 1428
(Workshop by Dept.: 08 November 2007/27 Shawwal 1428)

International Congress on Bone Marrow & Stem Cell Transplantation
13-15 November 2007/03-05 Dhu Al Qada 1428

The 7th IEA-EMRO Scientific Meeting "Epidemiology: Translating Research to Health Care"
27-28 November 2007/17-18 Dhu Al Qada 1428

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(Workshop by Dept.: 10 January 2008/01 Muharram 1429)

ACADEMIC DAYS

World Asthma Day
09 May 2007/22 Rabia Al Thani 1428

King Faisal Cancer Centre Research Day
30 May 2007/13 Jumada Al Awal 1428

7th Annual Surgical Research & Resident's Day
06 December 2007/26 Dhu Al Qada 1428

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WORKSHOPS

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20-21 March 2007/01-02 Rabia Al Awal 1428

2nd International Difficult Airway Management Workshop
10-11 April 2007/22-23 Rabia Al Awal 1428

Impact of Emerging Zoonotic Diseases on Human Health Workshop
15-16 May 2007/28-29 Rabia Al Thani 1428

Pediatric Infectious Diseases Seminars
23-24 October 2007/11-12 Shawwal 1428

Dental Implant Workshop
30 October-01 November 2007/18-20 Shawwal 1428

Point of Care Testing (POCT)
20-21 November 2007/10-11 Dhu Al Qada 1428

4th Annual AIDS Workshop
01 December 2007/21 Dhu Al Qada 1428

International Workshop: Minimally Invasive & Endoscopic Neurosurgery Workshop
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postponed

Pharmacotherapy Review Course
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01-06 September 2007/19-24 Shaban 1428

Projected Materials in Internal Medicine Course
01 November 2007/20 Shawwal 1428

3rd Antimicrobial Review Course
21-22 November 2007/11-12 Dhu Al Qada 1428

4th Advanced Pediatric Minimally Invasive Surgery Course
28-29 November 2007/18-19 Dhu Al Qada 1428

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للسعوديات فقط

(مؤسسة عامة)

إعــلان

يسر إدارة الإبتعاث والتدريب بالتعاون مع إدارة التمريض بمستشفى الملك فيصل التخصصي ومركز الأبحاث (مؤسسة عامة) أن تعلن عن رغبتها في إتاحة الفرصة للدراسة والتدريب في جامعة الملك سعود بن عبدا لعزيز للعلوم الصحية (كلية التمريض والعلوم الطبية المساعدة) للفتيات السعوديات والحصول على درجة البكالوريوس في علوم التمريض للفصل الدراسي القادم (**سبتمبر ٢٠٠٦**)

الشروط المطلوبة:

- سعودية الجنسية
- حاصلة على مجموع لايقل عن ٨٠٪ في امتحان الثانوية العامة (**قسم علمي**)
- لايكون قد مضى على تخرجها اكثر من ٣ سنوات
- لايقل مجموع المواد العلمية واللغة الانجليزية عن ٨٥٪
- إجتياز الاختبار والمقابلة الشخصية المعد من قبل (**كلية التمريض والعلوم الطبية المساعدة**)
- تفرغ كامل للدراسة وان تكون لائقة جسدياً

المستندات المطلوبة:

- طلب من المتقدمة برغبتها الانضمام والدراسة لدرجة البكالوريوس في علوم التمريض
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- يشترط لمن حصلوا على الشهادة الثانوية من خارج المملكة معادلتها وتصديقها من وزارة التعليم العالي
- ٤ صور شمسية
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- خطاب بموافقة ولي الأمر بانضمام المتقدمة للدراسة في كلية التمريض والعلوم الطبية المساعدة.

سيتم إجراء الفحوصات الطبية لمن يقع الأختيار عليهم في مستشفى الملك فيصل التخصصي ومركز الأبحاث. وعلى من يتم قبولهم بالبرنامج التوقيع على إقرار بالعمل لمدة لاتقل عن سنتان في مستشفى الملك فيصل التخصصي ومركز الابحاث بعد التخرج. أخر موعد لقبول الطلبات هو نهاية دوام يوم الأثنين ٦ رجب ١٤٢٧ الموافق ٣١ يونيو ٢٠٠٦

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About The Cover

A portrait of Abu Al Qasim Al Zahrawi from a Syrian stamp issued in 1964.

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information for authors

The Editors of the Annals of Saudi Medicine welcome contributions from our readers. The Annals will consider for publication manuscripts from any part of the world, but most particularly manuscripts that would be of interest to readers in the Middle East. We publish scientific reports on human subjects in the form of original articles, brief reports, case reports and letters. We also accept review articles, special communications and editorials. All submissions are subject to review by the Editorial Board and by referees in appropriate specialties.

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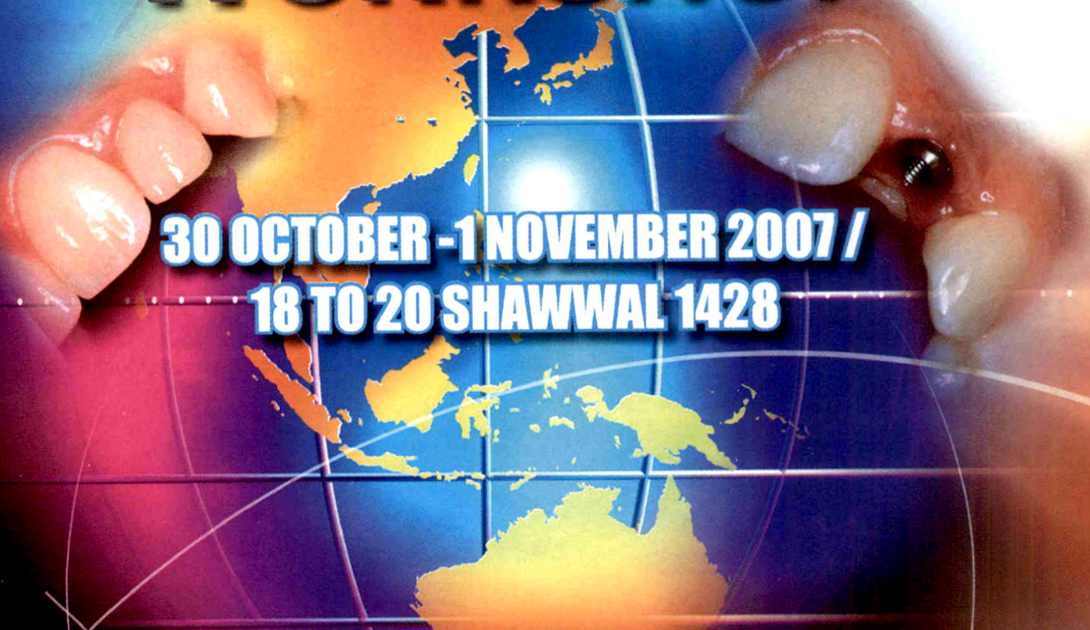

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summary of original articles

OPHTHALMOLOGY

Simple excision alone versus simple excision plus mitomycin C in the treatment of pterygium

Mikaniki and colleagues compared relapse rates of pterygium in 100 patients operated on with simple excision alone with 300 patients operated on with simple excision plus topical mitomycin C 0.02% eye drops four times a day for 4 days after the operation. After 5 years of follow-up, relapse occurred in significantly fewer patients in the mitomycin C group (31% vs. 1%, $P<0.0001$). The mean time to recurrence was significantly longer in the mitomycin C group (3.83 years vs. 4.96 years, $P<0.0001$).

RADIOLOGY AND SURGERY

Biliary ascariasis: the value of ultrasound in the diagnosis and management

Over 5 years, Al Absi and colleagues made a sonographic diagnosis of biliary scariasis in 46 Yemeni patients. The parasites were present in the main bile duct in 23 patients, in the gallbladder in 12 patients, in the intrahepatic duct in 6 patients, in the main pancreatic duct in 4 patients and as an intrahepatic asscess in one patient. Sixteen patients underwent surgery, 20 patients were treated medically and in 10 patients worms were extracted by endoscopic retrograde cholangiopancreatography. Follow-up ultrasound was effective in confirming the diagnosis and monitoring management.

ENDOCRINOLOGY

Assessing glycemia in type 1 diabetic patients using a microdialysis system for continuous glucose monitoring

Radman and colleagues randomized 52 type 1 diabetic patients on twice daily NPH and pre-meal aspart insulin into two groups, one which continued with the same regimen (n=26) and one that replaced basal insulin with glargine at bedtime (n=26). At the beginning and 4 months after randomization, 48-hour registrations were taken with a microdialysis-based continuous glucose monitoring device. Analysis of data from the device provided additional information about glycemia other than HbA1c and self-monitoring of glucose, such as activity profile and time spent outside the normoglycemic range.

INFECTIOUS DISEASE

Tuberculosis treatment outcome in a tertiary care setting

Bukhary and Alrajhi describe 535 cases diagnosed and treated for *M. tuberculosis* infection over a ten-year period at a major tertiary care hospital in Saudi Arabia. Isolated pulmonary tuberculosis was identified in 26.4%, extrapulmonary tuberculosis in 63.3% and combined pulmonary and extrapulmonary disseminations in 10.3%. Comorbidities were noted in 52%. Immunosuppression was found in 34%. The cure rate was 82%. Overall mortality was 18% and was highest in patients with disseminated tuberculosis. Despite tertiary care support, complicated tuberculosis carries a high mortality. Earlier diagnosis and complete appropriate chemotherapy are essential to improve outcomes.

PEDIATRICS

Extreme elevation of the erythrocyte sedimentation rate in children

In 2540 ESR measurements performed in children, Abbag and colleagues found 99 that were ≥ 100 mm/hr. Infection was the most common cause of elevated ESR (49.5%), followed by connective tissue diseases (26.3%), malignancy (12.1%) and renal diseases (8.1%). In comparison with 145 children with an ESR < 100 mm/hr and mild infections, mean leukocyte counts were higher in the patients with elevated ESR and mild infections. In children with connective tissue diseases in both groups, children with elevated ESR had significantly lower mean hemoglobin values.

OBSTETRICS AND GYNECOLOGY

Sonographic fetal weight estimation using femoral length: Honarvar equation

In 500 pregnant women at 36 weeks gestation, Firoozabadi and colleagues used real-time sonography to measure femoral length and then estimated the weight of the fetus using the Honarvar 2 equation. The estimated fetal weight correlated significantly with the actual birthweight. The authors recommend the Honarvar equation for estimating fetal weight in Iranian fetuses.

special communication

Medical Education at the Crossroads: Which Way Forward?

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Over the last 30 years, several changes have been introduced in medical education including the introduction of new contextualized approaches to instruction (e.g., problem-based learning [PBL]), the use of multimedia to enhance self-directed learning, the use of an integrated curriculum to address basic and clinical sciences, and the introduction of new formative and summative assessment tools that match with the curriculum changes. However, several challenges face medical education and need to be carefully researched. The list may be long and these challenges may vary depending on the needs of local and international health systems, the availability of resources, the vision of medical leaders and how they see these challenges and their impact. This paper discusses a number of challenges facing medical education including the selection of medical students and the validity of selection tools, students' learning skills, what makes a good medical curriculum, and the challenges facing a PBL curriculum.

"Medical education at the crossroads" was the title of an article published in the Proceedings of the Institute of Medicine of Chicago approximately 34 years ago by an American physician, Paul Rhoads.[1] This challenging topic emerges every 20 or 30 years to stimulate leaders and educators to assess the direction of medical education, the current needs of the medical profession and what medical education can do to fulfill these needs. Medical education is conceptualized as the complex process by which a medical student is changed from a medical school applicant to a medical school graduate. In other words, from unknowing to knowing, from unskilled to skilled, from layman to professional, from medical student to physician.[2] Although these changes were described by Socrates more than 400 years before the Common Era, it is of interest to note that since the time Dr. Rhoads wrote his paper, several changes have taken place in most medical schools. For example, dissection of the whole cadaver used to be an essential component of every medical curriculum. Discipline-based rather than an integrated teaching approach was used in most schools and teaching was mainly based on lectures. At that time, problem-based learning (PBL) was only known in two or three medical schools and information technology and medical informatics were unknown. Furthermore, the importance of role models in medical schools was not clearly defined.

Medical education comprises complex processes including faculty selection of students, learning and acquiring information by medical students, teaching by the faculty members and governance by the education unit. How these processes are interrelated to form medical education as we know it today warrants critical assessment.

The aim of this article is to address key changes and critical issues facing medical education including: (1) the selection of medical students, (2) the art of learning, (3) what makes a good medical curriculum, and (4) challenges facing a PBL curriculum. A review of the medical literature shows that these issues are not adequately addressed. However, these issues should constitute a framework for medical educators and should stimulate researchers to target them.

Selection of medical students

At a pre-conference workshop conducted at the Australian and New Zealand Association for Health

Professional Education (ANZAME; http://www.anzame.unsw.edu.au) annual conference, held in Australia in June 2006, the validity and reliability of the selection processes used in the Australian and New Zealand universities were addressed. The workshop covered different tools used in selecting graduate-entry students such as the Graduate-entry Medical Schools Admissions Test (GAMSAT; http://www.gamsat.acer.edu.au/) and standardized interviews. Also the selection of school leavers (students who do not have a prior university degree) by using the grade point average (GPA), the Undergraduate Medicine and Health Sciences Admission Test (UMAT; http://www.acer.edu.au/tests/university/umat/) and standardized interviews. The workshop raised a number of questions such as do we have evidence that those scoring higher in the GAMSAT and the interview will be better practitioners? Are we selecting students who will be good for the course or students who will be good for the profession and career after graduation? And what is the exact validity of the selection tools?

Medical schools in the USA and the Association of American Medical Colleges (AAMC; http://www.aamc.org) have undertaken some useful research addressing these questions. With the introduction of a revised Medical College Admission Test (MCAT; http://www.aamc.org/students/mcat/) in 1991, the Association of American Medical Colleges (AAMC) has been investigating the extent to which MCAT scores predict success in medical schools and how that could supplement the predictive power of the undergraduate grade point average (uGPAs). The study found that MCAT scores were better predictors of the United States Medical Licensing Examination (USMLE) Step scores than were uGPAs, and the combination did little better than MCAT scores alone.[3] The probability of experiencing academic difficulty or distinction tended to vary with MCAT scores. MCAT scores were strong predictors of scores for all three Step examinations, particularly Step 1. The author concluded that MCAT scores could replace the need for uGPAs in predicting Step scores. Once again there is no answer to the question whether these results guarantee that students will be better practitioners after graduating.

The question of who will be studying medicine in the future has recently been raised by the editor of *Academic Medicine*.[4] The Editor presents a case on the basis of the AAMC report[5] and argues that the cost and duration of a medical education could deter some potential medical school applicants from pursuing a career in medicine and these factors could affect students from families in lower socioeconomic groups including minority groups, migrants, and aboriginal students. One of the solutions to this problem is to review the length of the medical school curriculum, which should be shortened by one year. Do we have evidence that teaching medicine in five or six academic years produces better doctors than those taught medicine in three or four years? The experience at McMaster strongly supports the notion of a three-year medical curriculum for graduate-entry students.[6]

How important is reducing the medical curriculum to three years instead of four or five? What is the economic impact of these changes? How important are these changes, particularly when there is a large demand and shortage in the workforce in Australia, the UK, USA and several other countries? What type of curriculum should be used as we reduce the number of academic years? What will be the ideal approach to select medical students to enroll in these courses?

Although we do not have definite answers to these questions and these issues were not addressed by researchers, we do need to start testing possible solutions and finding out what exactly makes a good graduate and how we can use the curriculum and undergraduate training effectively to assess the outcomes and the impact of these changes. Collaboration in this area is vital and we should learn from McMaster's expertise.

Another important issue in this regard is the responsibility of the Faculty of Medicine towards education in high schools and middle years. We cannot get good students just by having good selection tools. We need to invest in students who are willing to study medicine and we should share in the process of their education at an earlier stage. This type of partnership has been reported from several American universities.[7,8,9] Along these lines, over the last three years, we have undertaken a project with 6 schools in the eastern region of Victoria. This project represents a partnership between the University of Melbourne and six schools. The aim of the project is to introduce PBL in the middle years as a teaching tool and assess the usefulness of the project and its impact on students' learning and staff development.

The art of learning

The effect of the rapid explosion of research publications in the literature over the next 10 or 15 years is well described by Miser. He stated, "If physicians would read two articles per day out of the six million medical articles published annually, in one year, they would fall 82 centuries behind in their reading".[10] One of the main objectives of PBL curricula is to enhance students' self-directed learning and construction of information. With the reduction in the number of lectures and the encouragement of students to deal with uncertainty and discuss cases with no prior knowledge about case content, the need for self-directed learning becomes essential. However, how do we know if students are really searching for new information and have not asked students' from previous years to give them the learning issues of the cases? Some studies have reported that students' self-study has dropped constantly in the last 5 years following the introduction of PBL and students' preparation for tutorials have been below the desired standards.[11] For example, students tend to focus on the diagnosis rather than using the case as a learning vehicle. Do students really search for information? Should we give them the resources for each week or leave them to find their own resources? What evidence do we have that PBL curricula foster self-directed learning? Should we teach students how to search for new information?

There is evidence that different students have different styles for learning and medical students do use a wide range of learning styles during the medical course.[12] Understanding these needs is essential and course designers should include a wide range of teaching strategies that enables the learning needs of students e.g., PBL classes, seminars, lectures, computer-aided learning resources, online-resources, clinical rounds, practical classes, etc. It is important to consider these key principles as we discuss what will make students' learning more efficient; the following keys are proposed:

Key 1: Learning is more efficient when the gaps between theory and practice disappear. The combination of authentic learning and theory instruction should better enable students to relate theory to practice.

Key 2: Learning is more efficient when the learning experience has meaning to the learner and the learner is able to construct their new knowledge.

Key 3: Learning is more efficient when the learner is able to identify their learning needs and turn their learning practices into an enjoyable experience.

Key 4: Learning is more efficient when the learner receives constructive feedback that builds them up, enables them to deepen their understanding of new concepts, helps them to identify areas of weaknesses and strengths in their learning, and guides them to support systems available to them.

Key 5: Learning is more efficient when the learner is actively involved in the learning process and is motivated to share knowledge with others.

Key 6: Learning is more efficient when the learner is encouraged not just to master knowledge, use it and explore different aspects of new concepts, but also empowered to discover things and learn how to think in a creative way. The university should adopt a culture and learning environment that encourages students to discover new things.

Key 7: Learning is more efficient when the learner is able to see the big picture and the fine details, ask open-ended questions, provide justification for their views, weigh the evidence for different hypotheses, use evidence-based approaches and use communication effectively to achieve their objectives.

The faculty needs to invest more time in supporting students' learning. We need students to explore better ways of learning and supporting them on issues such as: How can I read a chapter from a scientific textbook? How can I get the best out of a lecture? How can I become an effective scribe in a PBL tutorial? How can I change my learning to become more strategic and deeper? How can I use a reflective journal to enhance my skills and change my attitude? What actions do I need to do to achieve my goals?

Usually the faculty spends more time on teaching disciplines in basic and clinical sciences, but not on students' learning and how they can develop their self-directed learning.

What makes a good medical curriculum?

Is there a recipe for course designers to help them develop a good curriculum? What will make a good medical curriculum? Many find the term "curriculum" rather confusing. Different people perceive a medical curriculum in different ways depending on their role, the context in which the concept is used, and their perception of the scope of the term "curriculum". In fact, the term "curriculum" refers to a wide range of images and characteristics rather than a narrow definition. These characteristics may include:

- Curriculum as a subject matter - a body of content to be taught.
- Curriculum as learners' experiences
- Curriculum as goals, objectives and outcomes.
- Curriculum as learning culture
- Curriculum as the individual capacity and opportunities to participate.
- Curriculum as a framework for key concepts and principles.

- Curriculum as skills, attitudes and competencies to be achieved by learners.

Curriculum is also complemented by staff training and development, student support programs, evaluation and feedback, formative and summative assessment and research projects to enhance different aspects of medical education.

A good curriculum focuses on main concepts. It allows students to engage in a number of activities and learn through case scenarios. It enables students to receive feedback and reflect on their learning experiences. It also provides an opportunity for learners to enhance their competency in clinical skills, enables the integration of medical humanities[13] and provides learners with keys for professional success. A good medical curriculum covers patients and community needs, and prepares students for the challenges they will face when they graduate, such as the need for continuing medical education, effective use of medical informatics, contribution to professional development and the ability to pass medical licensing examinations and practice medicine in other countries. The use of clinical cases such as the one mentioned in this article is useful in complementing undergraduate medical curricula, particularly when they are written with specific educational objectives.

Challenges facing PBL curricula

The effect of PBL on the professional competencies of its graduates has recently been demonstrated[14]; graduates of a PBL course considered themselves to have much better interpersonal skills, better competencies in problem solving, self-directed learning, information gathering, and better task supporting skills. The findings of this study suggest that PBL not only affects the PBL-related skills and cognitive domains, but also the more general work-related skills that are deemed essential in professional practice.[14] Two other studies are consistent with these results and have demonstrated that graduates of PBL schools display better interpersonal skills.[15-16]

However, a comprehensive review by Moust et al[11] raised a number of challenges facing PBL at Maastricht University. Reviewing the literature shows that a number of other researchers have raised concerns about similar issues.[17-20] These challenges could be summarised as follows:

* Students tend to deviate from PBL in the analysis of problems and synthesis of information or similar cognitive actions. They sometimes use shortcuts that interfere with the learning process. These changes, if not reversed by their tutors, have serious negative effects on the learning process and outcomes.

- Tutors in some courses move away from questions that challenge students' thinking process. They replace them with straightforward short lectures. In these courses, reflections about how to proceed in analysing or synthesizing the information become gradually ignored.

- Briefing sessions and tutor guides have become less process-oriented and more subject-matter focused. As a result, the facilitation questions in the tutor guides have become more focused on fine detail and factual knowledge. These changes have affected the discussion in PBL tutorials and turned tutorials to question-answer sessions. Consequently, students in these courses have become interested in gaining a copy of the tutor guides rather than using the tutorial time to discuss key issues in the case, ask good open-ended questions and identify their learning issues.

- Assessment does not match with the PBL philosophy and is more focused on factual knowledge rather than testing understanding, cognitive skills (e.g., generating hypotheses, providing justification, making decisions on the basis of available evidence), interpersonal and communication skills as well as self-directed learning. What tools could we use in the assessment of non-cognitive competencies such as interpersonal skills, empathy, integrity and effective communication?

- Because of an inadequate staff-student ratio, the number of students in the tutorial group has increased in some courses to 19 students per group. This increase in the group size could adversely affect group dynamics, the contribution of students to the discussion, and the learning process. As a result, the process of hypotheses generation becomes less fluent and case discussion more superficial.

These challenges necessitate proper management actions. Directors of medical education should be prepared with preventive measures. For example, they should introduce refresher courses covering these challenges and hands-on facilitation skills[21], continuous mentoring of PBL tutors and providing constructive feedback, and use the briefing/debriefing sessions as an opportunity to discuss the facilitation processes, how tutors manage difficult situations and how they could enhance their facilitation skills. The use of good role models in PBL courses has been shown to be useful in constructing a learning environment and should be encouraged by leaders in medical schools.[22] Medical directors who have successfully introduced PBL into their courses should be aware of these challenges and should give priority to the maintenance processes and measures that keep teaching and tutor facilitation skills up-to-date and of high quality.

Conclusion

Although significant changes have been introduced to medical education in recent years in most medical schools, there is evidence that a number of challenges have not been adequately addressed. These emerging issues/questions may include the validity and reliability of tools used in the selection of medical students. What evidence do we have that PBL curricula foster self-directed learning? What will make a good medical curriculum? What actions should we take to ensure better learning in the PBL structure? What is the use of good role models in teaching? What tools could we use in the assessment of non-cognitive competencies such as interpersonal skills, empathy, integrity and effective communication? These emerging challenges are not answered by current medical literature and represent gaps in our knowledge that need to be adequately addressed by research.

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original article

Simple excision alone versus simple excision plus mitomycin C in the treatment of pterygium

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BACKGROUND: Pterygium is a common ocular disorder throughout the world. The purpose of this study was to evaluate the efficacy of simple excision alone with or without topical mitomycin in the treatment of pterygium.
PATIENTS AND METHODS: This study was performed in two stages. In the first stage, from 1991 to 1994, 100 patients (group 1) were operated on with simple excision and in the second stage, from 1995 to 1999, 300 patients (group 2) were treated with the same procedure plus topical mitomycin (0.02% eye drops four times a day for 4 days after operation). All cases were followed for 5 years. The recurrence rate of pterygium in these two treated groups were compared.
RESULTS: The mean age of the subjects was 49±13 years in group 1 and 47±17 years in group 2. The clinical manifestations in these two groups were similar ($P>0.05$). After one year, relapse was seen in 21 cases (21%) in group 1 and in 3 cases (1%) in group 2. After five years, 31 cases (31%) in group 1 and 3 cases (1%) in group 2 had relapse ($P=0.0001$). The mean time to recurrence at five years for the simple excision group was 3.83 years (95% CI: 3.48 to 4.17 years) and for simple excision plus mitomycin C was 4.96 years (95% CI: 4.91 to 5.0 years) ($P<0.0001$).
CONCLUSION: Instillation of mitomycin C eye drops appears to be safe in the treatment of pterygium.

Pterygium is a common ocular surface disorder of the subconjunctival tissues. It creates symptoms of irritation, foreign body sensation and lacrimation, cosmetic disfigurement, and functional problems such as reduced visual acuity, diplopia and problems fitting contact lenses. A variety of surgical procedures have been described, but the recurrence of pterygium still remains a major complication. Recurrence rates vary from procedure to procedure. One of the major limitations of pterygium excision is the high rate of postoperative pterygium recurrence. The reported postoperative recurrence rate of pterygium excision alone ranges from 56% to 89%.[1-3] Simple excision is reported to be associated with recurrence rates 30% to 100%[1] and excision by the bare sclera technique has recurrence rates of 5% to 89%.[2,3] Even conjunctival autografting to cover the bare sclera is associated with recurrence rates of 2% to 39%.[4,5] Therefore, various adjuvant therapies have been used to prevent recurrence of pterygium after excision like irradiation, argon and excimer laser, thiotepa and mitomycin C application. Various studies have reported the efficacy in reducing the recurrence rate following pterygium surgery.[6-9] Although the recurrence rate has been reduced after use of mitomycin C, there are reports of serious vision-threatening complications following mitomycin C application.[10-12] In the present study we compared the efficacy, of simple excision versus simple excision plus topical mitomycin C for the treatment of pterygium.

PATIENTS AND METHODS

This prospective follow-up study was performed at the Department of Ophthalmology of Babol Medical University in Iran in two stages. In stage 1, from 1991 to 1994, 100 patients were treated with simple excision of pterygium and in stage 2, from 1995 to 1999, 300 patients were treated with simple excision plus mitomycin C 0.02% drops four times a day for 4 days. The demographic features and clinical manifestations of the patients were recorded. All cases were treated as outpatients. The ethical committee approved the study and all the patients gave their informed consent. Anesthesia was established with tetracaine eye drops. At first, the base of the pterygium was separated from the sclera and then the corneal part was isolated using blade number 15. After the operation, the eye was covered by *Terramycin* ophthalmic ointment. In group 2, mitomycin C eye drops 0.02% (lyophilized mitomycin mixed into artificial tears), one drop four times per day for 4 days were applied after operation. Both groups were followed on day 7, 14, 30, and for intervals of every 6 months for 5 years. Data were analyzed with SPSS. The chi square test or Fisher's exact test were used to compare categorical variables between the two groups. Time to recurrence for the two groups was calculated using the Kaplan-Meier method with differences assessed using the log-rank test.

RESULT

The mean age of the patients was 49±13 years in group 1 and 47±17 years in group 2. Fifty-three patients (53%) in group 1, and 159 patients (53%) in group 2 were males (Table 1). Pterygium in all cases in group 1 was unilateral. Pterygium in 290 cases in group 2 was unilateral and in 10 cases (8 males and 2 females) was bilateral. All pterygium originated from the nasal side. Photophobia, lachrimation and foreign body sensation were seen in all cases. Irregular strabismus was not seen in either groups. After treatment, all cases suffered from photophobia. Among 100 cases treated in group 1, recurrence was seen in 31 (31%), but recurrence was seen in 3 (1%) cases treated in group 2 (P=0.0001). After only one year, recurrence was seen in 21 (21%) cases treated with simple excision versus 3 (1%) treated with simple excision plus mitomycin C. After 5 years, recurrence was seen in 31% cases treated with simple excision but in 1% treated with simple excision plus mitomycin C (Figure 1). The mean time to recurrence at five years for the simple excision group was 3.83 years (95% CI, 3.48 to 4.17 years) and for simple excision plus mitomycin C was 4.96 years (95% CI, 4.91 to 5 years)(P<0.0001). Mitomycin C was well tolerated in all cases. Intraocular pressure, corneal edema, cataract and infection were not seen in any case. Scleral necrosis was seen in two elderly cases (65 and 70 years old) and both were treated appropriately.

Table 1. Demographic features and clinical manifestations of the two groups.

Characteristics	Group 1 No (%)	Group 2 No (%)	*P* value
Sex			
Male	53 (53)	159 (53)	0.546
Female	47 (47)	141 (47)	
Clinical manifestation			
Unilateral	100 (100)	290 (96.7)	0.054
Bilateral	0 (0)	10 (3.3)	
Location of the lesion			
Nasal	100 (100)	300 (100)	1
Temporal	0 (0)	0 (0)	
Photophobia	100 (100)	300 (100)	1
Lacrimation	100 (100)	300 (100)	1
Foreign body sensation	100 (100)	300 (100)	1

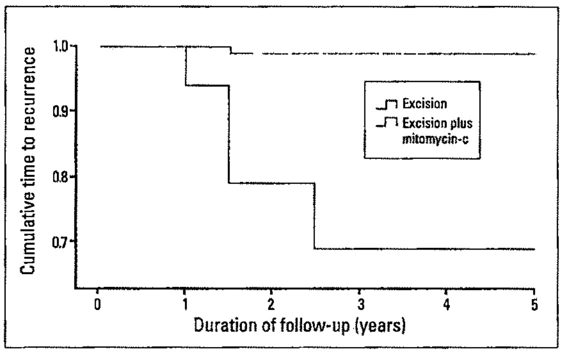

Figure 1. Kaplan-Meier survival curve depicting the time to recurrence among patients treated with simple excision alone or simple excision with topical mitomycin in the treatment of pterygium.

DISCUSSION

We found that with simple excision, the recurrence rate was 31% and with excision of pterygium plus mitomycin C, the recurrence rate was 1%. In other studies, postoperative application of topical mitomycin C four times a day for two weeks or twice a day for five days decreased the recurrence rates to 0% to 11%.[13-17] Prospective studies have also reported that single intraoperative scleral application of 0.1 mg/mL to 0.2 mg/mL mitomycin C for 3-5 minutes reduced the recurrence rates to 3.3%-12%.[18-20] Mitomycin C is an antineoplastic antibiotic with radiomimetic properties that selectively inhibits DNA, RNA and protein synthesis.[21] In the present study, the recurrence rate of 1% was compatible with the results reported in other studies,[6-8,10,12,13,15,16] but relatively lower that the result (20%) reported by Gupta and Saxena in India.[22] The low recurrence rate with mitomycin C in our study may be due to the older age of our cases or lack of environmental factors because the disease is more prevalent in a dry, dusty and smoky environment.[3] However, following the pterygium surgery our patients were not exposed more often to environmental irritants that might have initiated pterygium development. Postoperative or intraoperative application of mitomycin C has been associated with various postoperative complications.[22-25] Minor complications like ocular pain, photophobia, lacrimation and foreign body sensation are common in mitomycin C-treated patients as we saw in our cases. In this study, we have not found any serious complications in patients who received mitomycin C except in two cases, in which scleral necrosis gradually resolved. We hypothesize that single-drop instillation of mitomycin C at the end of surgery has greater penetration through the epithelium as the fibrin complex in the wound is not formed yet and it is likely to affect the entire population of potentially "pterygium proliferating cells". Additionally, this regimen is simple, quick, less toxic and independent of patient compliance. Whether the concentration of mitomycin in the eye drop and duration of the usage influence the outcomes of therapy or recurrence of pterygium should be clarified. In conclusion, mitomycin C 0.02% eye drops four times a day for 4 days after operation appear safe in the treatment of pterygium.

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original article

Biliary ascariasis: the value of ultrasound in the diagnosis and management

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BACKGROUND: Conventional methods of radiographic examination are often unsatisfactory for identifying worms in the biliary tract. Ultrasonography is a non-invasive, quick and safe procedure known to have diagnostic accuracy. We studied the ultrasonographic appearances of biliary ascariasis and the role of ultrasonography in diagnosis and management.

METHODS: In a prospective 5-year study, a sonographic diagnosis of biliary ascariasis was made on 46 Yemeni patients. The diagnosis was based mainly on sonographic appearances supported by clinical and laboratory results and proved by outcome of either surgical or medical management or spontaneous exit of worms. Follow-up ultrasound was performed for all patients to confirm the diagnosis and to monitor management.

RESULTS: Parasites were present in the dilated main bile duct in 23 patients, in the gallbladder in 12 patients, in the intrahepatic ducts in 6 patients, in the main pancreatic duct in 4 patients and as an intrahepatic abscess in one patient. The characteristic appearance of *Ascaris lumbricoides* was as single or multiple echogenic non-shadowing linear or curved strips with or without echoic tubular central lines that represent the digestive tracts of the worm. A spaghetti-like appearance was seen in 9 patients and amorphous fragments were seen in 2 patients. Sixteen patients underwent surgery, 20 patients were treated medically (including spontaneous exit of the worm in 7 patients without treatment) and in 10 patients worms were extracted by endoscopic retrograde cholangiopancreatography.

CONCLUSIONS: Follow-up ultrasound was found to be effective in confirming the diagnosis and monitoring management.

In endemic areas, which include Yemen, infestation with *Ascaris lumbricoides* is very common. It is a frequent cause of biliary tract diseases, which can be a serious public health problem in this part of the world.[1,2,3] Thus, early detection and treatment of this disease is of prime importance. The adult worm can migrate through the extra-hepatic biliary tree and may reach intra-hepatic ducts and the gallbladder causing biliary colic, obstruction, acute cholecystitis, acute cholangitis and hepatic abscess. *Ascaris* is also an etiological factor for acute pancreatitis and the overall mortality rate is 3%.[4] Conventional methods of radiographic examination are often unsatisfactory for identifying worms in the biliary tract. Ultrasonography, as a non-invasive, quick and safe procedure, has been known to have diagnostic accuracy in the work-up of biliary ascariasis.[5-12] Our study addressed the ultrasound appearances of biliary ascariasis and the value of ultrasound in confirming the diagnosis and assessing management outcome in a relatively large number of Yemeni patients.

METHODS

The study, which included 46 patients (30 female and 16 male), was conducted between May 2000 and June 2005 in the Kuwait University Hospital (Sana'a) and Sana'a Radiology Center. General abdominal sonography focusing on the liver and biliary system was performed for all patients referred with acute right hypochondrial or epigastric pain using Siemens Sonoline 450 and Logic 400 machines and a 3.5 MHz probe. The liver and biliary systems as well as the pancreas were scanned in longitudinal, transverse and oblique projections while patients were in the supine and lateral positions. Inclusion criteria were based on ultrasound findings suggestive of biliary ascariasis: straight or curved non-shadowing echoic cord-like structures with or without centrally hypoechoic tubes, the "spaghetti" sign, intrahepatic hyperechoic bundles, or a rounded hyperechoic pseudotumorous mass (Table 1). In addition, a sonographic appearance of sinuous motility or change of configuration of non-shadowing tube-like intrabiliary structures was an important inclusion diagnostic criteria.

Follow-up ultrasound was performed at 3 successive intervals: one week after initial ultrasound diagnosis for all patients, 2 weeks after initial treatment for 39 patients and after 2 weeks after repeated medical treatment for 3 patients. The clinical laboratory and management data as well as ultrasound follow-up outcome were recorded. The final diagnosis was based on established sonographic criteria and supported by the medical, surgical and endoscopic outcome as well as clinical and laboratory findings.

RESULTS

The ages of the 46 patients included in this study were between 6 to 67 years (mean and median age, 18 years). There were 30 females (63%) and 16 males (37%), including 4 women who were pregnant (3, 5, 6 and 7 months). About 60% of the patients resided in rural areas. The laboratory results showed raised serum alkaline phosphatase in 40% of patients, abnormal alanine aminotransferase in 30%, raised serum amylase in 12%, and leukocytosis in 90%. Ova or adult forms of *Ascaris lumbricoides* were seen in the stool of 91% of patients. Each case of biliary ascariasis was clinically acute. The diagnosis of biliary ascariasis was established incorrectly in one patient owing to excessive post-sphincterotomy pneumobilia. In 46 cases where biliary ascariasis was seen on ultrasound there were 23 cases with worms in the main bile duct and 12 cases with worms in the gallbladder. There were 6 cases with worms in the common bile ducts as well as in intrahepatic ducts, 2 in the right lobe and 4 in the left lobe (Table 2). In 4 cases worms were seen in the main pancreatic duct and in one case an intrahepatic complicated abscess cavity was seen. Ultrasound demonstrated common bile duct dilatation, which measured 9 to 20 mm, in 35 cases. In 2 patients parasites were present in fusiform, dilated extrahepatic ducts that were proved at surgery to be choledochal cysts (Figures 1, 2) with stones.

Table 1. Distribution and appearance of biliary ascariasis based on ultrasound findings.

	No. of patients	%
Distribution		
Main bile duct	23	50.0
Gall bladder	12	26.1
Common bile duct	6	13.0
Main pancreatic duct	4	8.7
With right hepatic lobe abscess	1	2.2
Ultrasound appearance		
Straight or curved non-shadowing echogenic strips (strips sign) with or without tube sign	34	73.9
Spaghetti sign (aggregates of multiple worms)	9	19.6
Intrahepatic hyperechoic bundles	1	2.2
Rounded hyperechoic pseudotumorous mass	2	4.4

Table 2. Clinical presentation of biliary ascariasis.

Signs	No. of patients	%
Recurrent biliary colic	26	57
Acute cholingitis	8	18
Acute cholecystitis	7	15
Acute pancreatitis	4	8
Liver abscess	1	2

Associated nausea or vomiting was seen in 90% and jaundice in 40% of patients.

In 34 out of 46 patients, the ultrasound showed a usual appearance of one or more non-shadowing tubular structures that were either straight or coiled or appeared as a thick echogenic strip with a central anechoic tube representing the digestive tract of the worm (Figures 3, 4, 5, 7, 8). In 9 patients the bile duct was so solidly packed with worms that no lumen was visible, with a spaghetti-like appearance of multiple worms seen side by side (Figure 6). In one patient ultrasound showed intrahepatic hyperechoic bundles (Figure 9a) and in two patients a hyperechoic, round pseudotumorous mass was seen (Figure 9b, 10). Follow-up ultrasound showed that these bundles were changing in size and appearance. Table 1 shows the distribution and appearance of ultrasound findings.

Serial follow-up ultrasound was performed to confirm the diagnosis and to evaluate management outcome. The first follow-up ultrasound performed for all patients one week after initial ultrasound diagnosis revealed changes in the configuration of parasites, confirming diagnosis in 32 patients. In 7 patients, there was spontaneous exits of worms from the biliary tree without treatment. The other 39 patients underwent different types of management. Thirteen patients were treated by anthelminitic drugs and 16 patients by surgery. Worms had to be removed from the biliary system by endoscopic retrograde cholangiopancreatography in

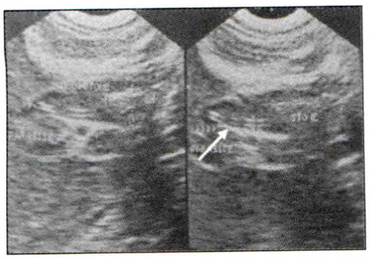

Figure 1. An oblique ultrasound scan of a 25-year-old female patient demonstrating fusiform expansion of the common bile duct (at surgery proved to be a choledochal cyst), which contains a rather large shadowing stone with an associated echogenic non-shadowing tubular structure (with anechoic linear center) proximal to the stone (arrow) and extending to the common hepatic duct.

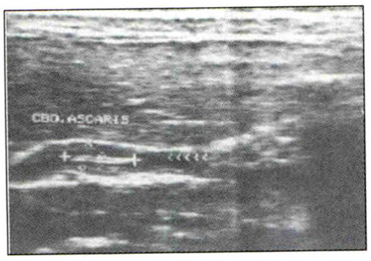

Figure 2. Another female patient aged 16 years with fusiform expansion of the common bile duct containing a non-shadowing, echogenic tubular structure with an anechoic linear center that showed active movement during examination.

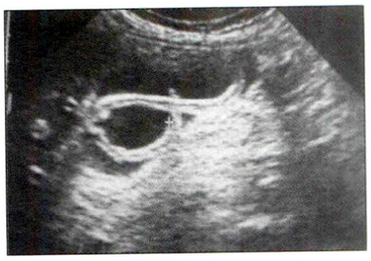

Figure 3a. Longitudinal ultrasound section of a relatively distended gallbladder containing a long echogenic, non-shadowing intraluminal tubular structure with a central anechoic linear area (the "inner tube" sign), representing the digestive tract of the worm.

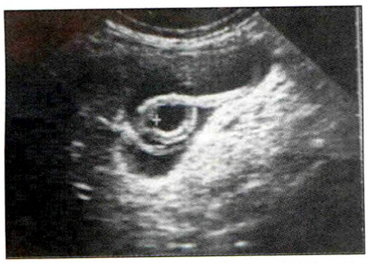

Figure 3b. Follow-up of Figure 3a shows change in configuration of the previously seen worm with the appearance of an additional smaller one posterior to it.

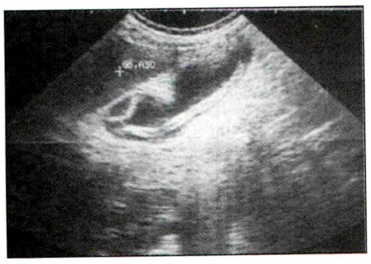

Figure 4a. Ultrasound scan of a gallbladder of another patient showing two intralumenal worms.

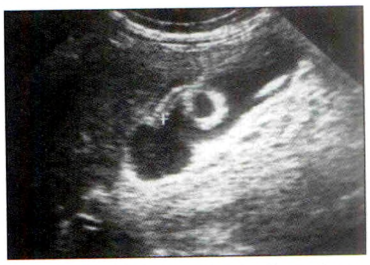

Figure 4b. Change in the configuration and positioning of the worm seen in Figure 4a on the control ultrasound, confirming the diagnosis.

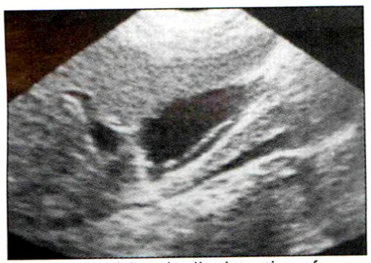

Figure 5a. A longitudinal section of gallbladder with the worm represented as an echogenic, non-shadowing tube-like structure (strip sign).

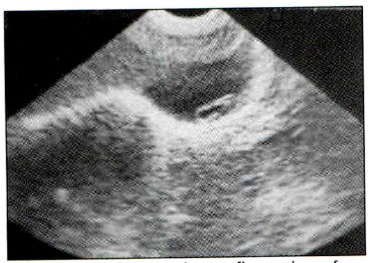

Figure 5b. Change in configuration of the worm in Figure 5a. with the worm folded on itself on the control scan, confirming the diagnosis.

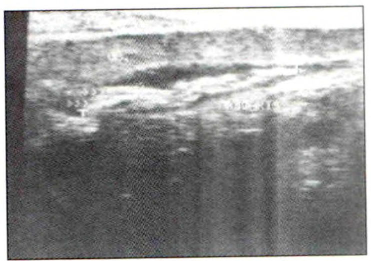

Figure 6. A longitudinal scan of a relatively contracted gallbladder showing several non-shadowing, overlapped, tube-like worms ("spaghetti" sign).

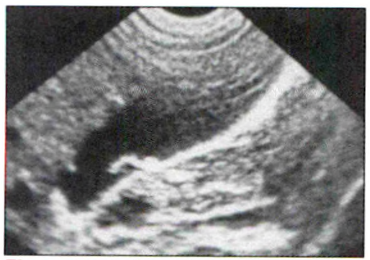

Figure 7a. In this patient, the gallbladder shows short non-shadowing hyperchoic curved strips that become ring-like in Figure 7b.

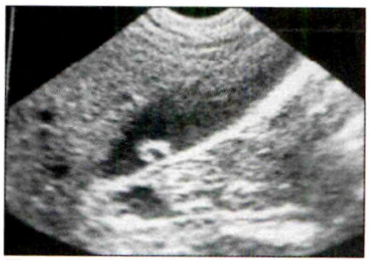

Figure 7b. The curved strips in Figure 7a have become ring-like.

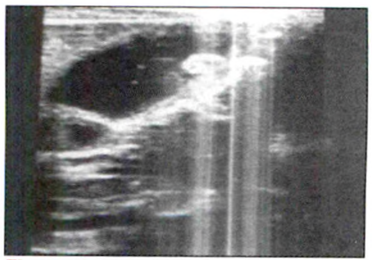

Figure 8. A longitudinal section of the gallbladder of a 15-year-old female patient shows a comma-shaped worm that exhibits active movement during ultrasound examination.

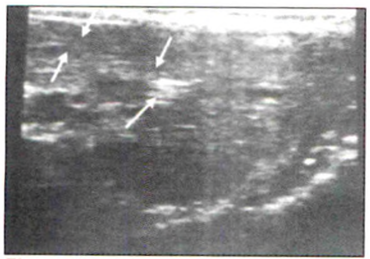

Figure 9a. A transverse scan through the left hepatic lobe shows a dilated intrahepatic duct that is packed with worms, producing an amorphous appearance and some worms in the form of a bolus.

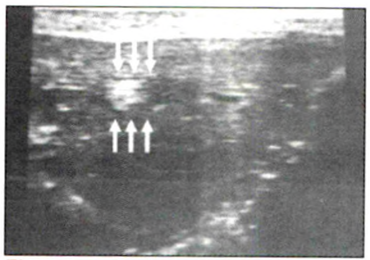

Figure 9b. Another transverse scan through the left hepatic lobe showing a dilated intrahepatic duct packed with worms in the form of a bolus.

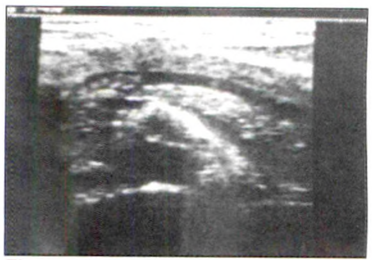

Figure 10. An ultrasound scan through the pancreas showing a worm bolus in the proximal segment of the dilated pancreatic duct.

10 patients. A second follow-up ultrasound performed 2 weeks after treatment for all patients showed a failure of management in 3 patients who underwent repeated medical management. In those patients a third follow-up ultrasound was normal 2 weeks later.

DISCUSSION

Ascaris lumbricoides is the largest intestinal roundworm and the most frequent of human helminthic parasites. It is endemic in third world countries, including Yemen, where poor health standards, low socioeconomic status and geoclimatic conditions influence the parasite prevalence in these parts of the world.[1,2,3]

The commonest extraintestinal manifestation of the worm is the biliary system, as it can easily gain entry into the common bile duct via the ampulla of Vater, which usually provokes biliary colic, fever, acute cholangitis and obstructive jaundice although asymptomatic cases are described.[4,5] Trans-abdominal ultrasound is a reliable modality for the diagnosis and post-therapeutic surveillance of biliary ascariasis. Several studies have discussed the sonographic findings of the roundworm in the biliary tracts and gall bladder.[6-13] Common findings have been described by Khuroo et al.[6] Linear or curvilinear thick, echogenic, non-shadowing structures with central anechoic longitudinal tubes are typical of ascariasis. The "inner tube" or the "double tube sign" implies the visualization of the hypoechoic alimentary canal of the worm. The worms are often seen as one or more non-shadowing, tube-like echoic structures, which may be straight or coiled (strip sign). Overlapping coiled or aggregates of worms may have an appearance like spaghetti. Dilatation of the common bile duct with or without a distended gallbladder is the next most common finding. However, when the lumen is packed solid with worms, especially if the solidity appears amorphous, a dilated bile duct could be missed. Intrahepatic duct boluses and bundles give a pseudotumorous appearance,[14,15] but acute clinical features, age and socioeconomic status should give a clue to the correct diagnosis. In addition, boluses should shrink. Worms in the gallbladder lumen are less common,[16,17] but in our study they were relatively common findings. The end-on appearance of the intraductal worm on transverse view is useful to solve any doubt of diagnosis on longitudinal view.[18] In our study young women were predominantly affected, although young children are most affected by *Ascaris* infestation with less biliary incidence, which may be due to the narrowed ampulla and lumen of biliary channels in children. One patient was false positive due to extensive biliary gaseous shadowing as post-sphincterotomy status. Pregnant patients may present with biliary parasites as seen in four cases in our study, and ultrasound was very helpful in their management. In addition, worms can complicate existing biliary duct anomalies as seen in our study of two incidentally found fusiform choledochal cysts (proved at surgery). About one fourth of our patients had associated intraductal or gallbladder stones, but there is evidence that biliary ascariasis causes intrahepatic stones.[12] Serial follow-up ultrasound demonstrated a change in the configuration of the worms in the majority of our patients and was a confirmative diagnostic factor. In addition, follow-up ultrasound showed complete disappearance of the worms from the biliary system of all our cases at the end of management. Thus, serial follow-up ultrasound was found to be very effective in confirming the diagnosis of biliary worms and has an important role in assessing their management outcome.

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original article

Assessing glycemia in type 1 diabetic patients using a microdialysis system for continuous glucose monitoring

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BACKGROUND: Continuous glucose monitoring systems can monitor moment-to-moment changes in blood glucose concentration, which cannot be detected by intermittent self-monitoring. Continuing monitoring systems may lead to improved glycemic control. We evaluated a microdialysis technique for improving glycemic control in type 1 diabetes patients treated by different means of basal insulin substitution.

PATIENTS AND METHODS: Fifty-two type 1 diabetic patients on twice daily NPH and pre-meal aspart insulin were randomized in two groups: the continuation of NPH (n=26) (group 1) or once daily glargine (n=26) (group 2). 48-hour *GlucoDay* registrations were started at the beginning and after 4 months.

RESULTS: At baseline, time spent in the euglycemic range (glucose between 3.9 and 8.0 mmol/L) was 37.96±6.81% for the NPH group and 35.83±6.24% for the glargine group. At endpoint, time in the euglycemic range increased in both groups (51.02±7.22% and 57.29±10.27%, $P<0.001$ vs. before treatment for both groups). Time spent in the hypoglycemic range (glucose <3.9 mmol/L) was 9.98±2.57% for the first group and 10.24±3.55% for the second group at baseline. At endpoint, time in the hypoglycemic range decreased in both groups (8.00±2.13% and 6.59±2.04%, $P<0.001$ vs. before treatment for both groups).

CONCLUSION: The analysis of the *GlucoDay* data gave us information about glycemia other than HbA1c and self-monitoring of blood glucose, such us a peakless activity profile and the lower percentage of time spent in the hypoglycemic range in the glargine-treated group.

Worldwide, the number of cases of diabetes mellitus is expected to increase exponentially, with current estimates suggesting an increase from 171 million in 2000 to 371 million sufferers by 2030.[1] In Croatia, type 2 diabetes mellitus accounts for about 90% of cases and type 1 diabetes mellitus for about 7%.[2] To prevent or delay the onset of microvascular complications, intensive insulin therapy is needed and recommended for treatment of type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) was designed to demonstrate the importance of intensive care for optimal glycemic control to reduce the risk of developing microvascular complications.[3] In broad terms, for every 1% fall in glycosylated hemoglobin (HbA1c) there is a reduction in microvascular risk by about 25%, irrespective of whether the patient has type 1 or type 2 diabetes.[4] The targets for blood glucose control are now much clearer. There are no thresholds within the diabetic range of blood glucose for risk of microvascular complications.[5] To reduce risk, the goal should be to achieve normal blood glucose levels.

The assessment of blood glucose can be done in various ways. Continuous glucose monitoring systems have considerable potential for monitoring moment-to-moment changes in blood glucose concentration which cannot be detected by intermittent blood glucose self monitoring, and may lead to improved glycemic control.[6,7,8] NPH is no longer considered as only basal replacement insulin in type 1 diabetes because of the risk of nocturnal hypoglycemia.[9,10,11] The novel recombinant insulin analog insulin glargine is a modification of human insulin in which two arginines are added to the B-chain and glycine is substituted for asparagine at the A21 position of the insulin molecule. These changes cause a shift of the isoelectric point to a neutral pH, precipitation at physiologic tissue pH, and increased hexamer stability, resulting in delayed absorption and a flat profile after injection, compared with the shorter duration of action and early peak of NPH insulin.[12]

To assess glycemia in type 1 diabetics treated by two different basal insulin replacement options we used *GlucoDay*, a microdialysis-based continuous subcutaneous glucose monitor that collects glycemia values every 3 minutes and thus enables calculation of parameters.

PATIENTS AND METHODS

The study was approved by the local ethics committee, and participants gave written informed consent. All patients with type 1 diabetes mellitus (fasting C-peptide concentration<200 pmol/L), classified according to the revised American Diabetes Associations guidelines,[13,14] admitted to the Day Care Hospital of the Clinical Hospital Split in Croatia, during January 2005, were included. All 52 type 1 diabetic patients were educated on treatment skills and changes in their daily lifestyles in the course of a 5-day educational program. They took active part in self-monitoring, exercise, menu planning and assessment of their own participation in the treatment of their disease. Initially, they were treated with a combination of three daily doses of a fast-acting analogue aspart insulin pre-meal and two daily doses of NPH insulin. After a 5-day educational program in Day Care Hospital, the first 26 patients continued their previous insulin regimen (group 1), and other 26 patients (group 2) were asked to replace basal insulin in the form of glargine at bedtime. Endocrinologists assisted patients in titrating the dose of the basal insulin to achieve fasting glucose values of 4.4-6.6 mmol/L, whilst avoiding hypoglycemia. Subjects previously using twice-daily NPH and randomized to receive insulin glargine were advised to reduce the insulin glargine dosage 10% compared with total NPH dosage. Endocrinologists titrate insulin glargine according to a treat-to-target algorithm.[15] The titration period was continued until adequate glycemic control in the endocrinologist's judgment had been achieved. Insulin glargine is a clear solution and is easily distinguished from NPH insulin, requiring an open-label design. The aspart insulin was used in both groups as bolus insulin during the whole observation period.

From the beginning of the study and after four months, we used a microdialysis-based continuous subcutaneous glucose-monitoring device (*GlucoDay*, A. Menarini Diagnostics, Florence, Italy) in all patients. The microdialysis probe of the *GlucoDay* was inserted subcutaneously in the periumbilical region. The *GlucoDay* device consists of a peristaltic pump that pumps Dulbecco solution at a rate of 10 microL/min along the microdialysis fiber (0.17 mm internal diameter and 18.000 Dalton molecular weight cut-off) and transports the dialysate derived from the subcutaneous interstitial fluid to the glucose sensor. The glucose sensor (immobilized glucose oxidase) takes a glucose measurement from the dialysate every second and stores an average value every 3 minutes until the device is removed. The lag time between subcutaneous and intravenous glucose values has been estimated to be less than 3 minutes.[16] Before insertion of the *GlucoDay* device, the sensitivity of the glucose sensor was checked in vitro using a standard D-glucose solution (90 mg/L), which gives a signal of 6 to 40 nAmp. Subcutaneous glucose was monitored every 3 minutes via the device. Blood glucose concentration was calculated from the data collected by the device (which measured glucose concentrations in the dialysate, expressed as nAmp) by calibration with the capillary values 120 minutes after probe insertion and 10 minutes before end of monitoring. When calibrating by the capillary value, the correlation coefficient obtained was $r=0.97$. No complications at the site of implantation were observed and there were no complaints of discomfort associated with *GlucoDay*. In addition, because of the ability of the system to communicate with a computer through an infrared port, online glucose variations were detected in real time, but we used the option of blind recording for patients to exclude any possible additional treatment intervention. Data collected from the patients included age (years), sex, body mass index (kg/m^2), diabetes duration (years), half-day glycemic profiles of capillary blood (mmol/L), and HbA1c (%).

Capillary blood glucose levels were analyzed by the enzymatic colorimetric method (Glucose GOD-PAP, Chronolab AG, Switzerland, on Olympus chemistry analyzer AU 400, Japan). All blood glucose probes for calibration were collected and managed by a nurse to avoid the subjective reactions of the endocrinologists to the patients. HbA1c was measured by ion-exchange chromatography based on separating hemoglobin adducts according to their charge (Chronolab AG, Switzerland). The normal values for capillary blood glucose were 4.2-6.1 mmol/L (coefficient of variation 1.4%), and for HbA1c were 4.2-6.2% (coefficient of variation 1.5%). The evaluation of the curves obtained with subcutaneous glucose recording, when compared to measurements on venous blood performed by the reference laboratory system showed a correlation coef-

Table 1. General characteristics of the type 1 diabetic patients treated with NPH two times/day (group 1) and once daily glargine at bedtime (group 2).

	Group 1 (n = 26)	**Group 2 (n = 26)**
Sex		
Female	10	14
Male	16	12
Age (years)	36.92±8.82	36.5±9.10
Duration of diabetes (years)	13.12±8.78	11.15±7.56
Body mass index (kg/m^2)	24.35±2.7	24.38±2.78
HbA1C before treatment	8.56±1.33	8.01±1.47
HbA1C after 4 months of treatment	8.00±1.04	7.13±1.08*

Values are expressed as means±SD. *P<0.05 for group 1 vs. group 2.

Table 2. *GlucoDay* registration glucose values for the type 1 diabetic patients treated with NPH two times/day (group 1) and once daily glargine at bedtime (group 2) before and after four months of treatment.

	Before treatment	**After 4 months of treatment**
Time spent in the euglycemic range (3.9-8.0 mmol/l) (%)		
Group 1	37.96±6.81	51.02±7.22*
Group 2	35.83±6.24	57.29±10.27*
Time spent in the hypoglycemic range (< 3.9 mmol/l) (%)		
Group 1	9.98±2.57	8.0±2.13 *
Group 2	10.24±3.55	6.59±2.04*

Values are expressed as means±SD. *P< 0.001, 4 months vs. before treatment.

ficient of 0.904 ($r^2=0.817$; $P<0.001$).The estimation standard error was -0.86 mmol/L and the error grid analysis gave values of 97% in the A/B zone, 2.5% in the C zone and 0.5% in the D zone.

The data was analyzed using SPSS for Windows (version 9.0., 2000). Results are expressed as the means±SD. Groups were compared by the t-test, with a two-tailed distribution and paired data.

RESULTS

There were no significant differences found for all baseline characteristics (age, duration of diabetes, BMI, HbA1c) as shown in Table 1. After 4 months there was no significant difference in BMI between the two groups. The duration of the study is one possible explanation for the lack of weight differences.

When comparing the two types of treatment according HbA1c, both groups showed a decrease in HbA1c ($P<0.0000005$ for the first group and $P<0.000001$ for the second group) (Table 1). At the end of the study, there was significant difference in the value of HbA1c between the groups ($P<0.005071$) (Table 1).

The values of HbA1c were significantly decreased within each group and were more homogeneous after treatment, which is shown from the reduced values of the standard deviations (1.33% to 1.04% for group 1; 1.47% to 1.08% for group 2). The biggest improvement was noticed in the group treated with a combination of three daily doses of aspart insulin and bedtime glargine insulin (Figure 1 and 2). Time spent at a glucose value between 3.9 and 8.0 mmol/L, confirmed by *GlucoDay*, increased in both groups (Table 2). Time spent at glucose below 3.9 mmol/L, confirmed by *GlucoDay*, decreased in both groups (Table 2). Both fiber insertion and the wearing of the device were well tolerated by all patients.

DISCUSSION

Studies in both pediatric and adult diabetic patients have conformed that intensive insulin therapy is needed and recommended to prevent the onset of microvascular diabetic complications.[3] Insulin secretion is a complex process requiring optimal coupling between glucose concentrations and insulin release. Insulin secretion is pulsatile, with release of bursts occurring every 4 to 6 minutes.[17]

At present, there are two models of physiological insulin replacement in type 1 diabetes mellitus. These models have in common the use of a rapid-acting insulin analog at each meal combined with basal insulin replaced in the form of either continuous subcutaneous insulin infusion or glargine once a day.[18,19,20]

In the past, ultralente or NPH insulin was commonly used to provide basal insulin concentrations.[10,11] More recently, glargine has been shown to be an effective basal insulin preparation.[15,21] Several studies, like our trial, have shown that when compared with NPH insulin, use of glargine results in comparable or lower HbA1c concentrations and a lower frequency of nocturnal hypoglycemia.[11,12,22]

Variation in glucose concentrations is frustrating to patients with type 1 diabetes and their health care providers.[23] An attempt to improve HbA1c in type 1 diabetes needs to incorporate assessment of glycemic variation. To measure glucose concentrations in two different basal insulin replacement options we used *GlucoDay*, which collects glycemia values every 3 minutes and thus enables us to calculate parameters. Continuous subcutaneous glucose monitoring can provide extremely useful

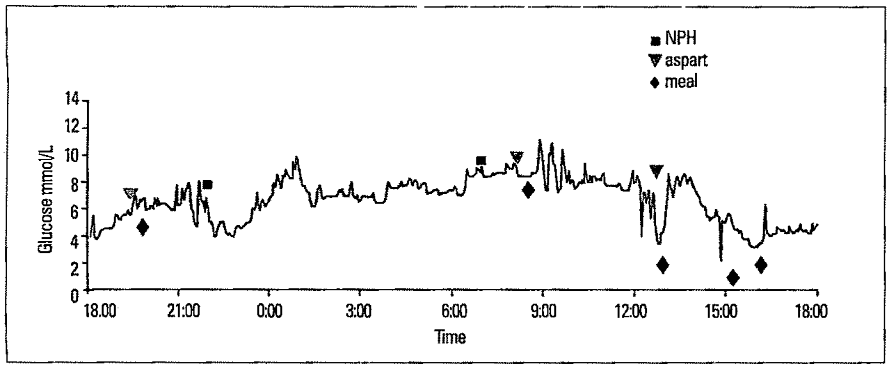

Figure 1. Example of *GlucoDay* registration showing glucose values in type 1 diabetic patient on two daily NPH doses and aspart insulin at each meal after 4 months of treatment.

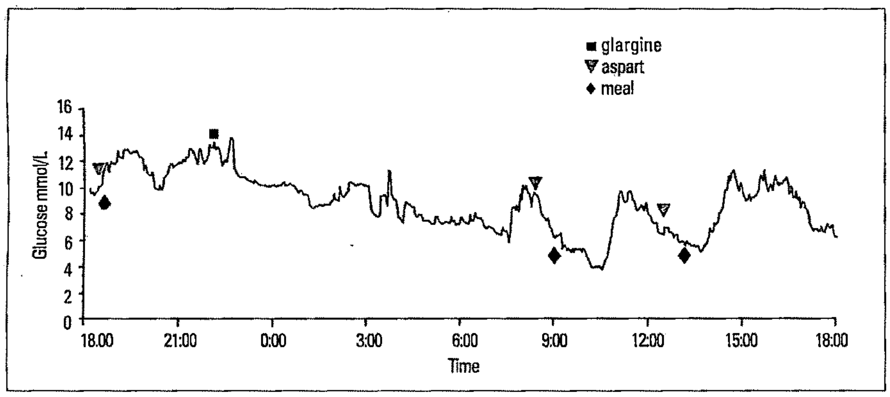

Figure 2. Example of a gylemic profile obtained with the *GlucoDay* device in type 1 diabetic patient on one dose of glargine and aspart insulin at each meal after 4 months of treatment.

information about an individual's glucose pattern and fluctuations during the day, which cannot be detected by intermittent blood glucose self monitoring.[24] This is particularly useful for detecting overnight glycemic excursions in intensively insulin-treated type 1 diabetic patients. Achieving HbA1c targets of <7 % HbA1c in type 1 diabetic patients in clinical practice involves long-term motivation and co-operation by patients and healthcare providers. Continuous glucose monitoring is an important adjunct to the overall care of the diabetic patient, particularly for the Day Care Hospital. Our findings demonstrated that the *GlucoDay* system was associated with little or no discomfort for the patient. It provided important information in real time that may lead to therapeutic adjustments, and the patient's glycemic control can be improved significantly.

It must be pointed out that glargine has a peakless time-action profile that lasts 24 hours, whereas NPH insulin has a distinct peak with a shorter duration of action.[25] Reviewing healthy subjects only, the analysis of within-day fluctuations of serum insulin levels shows that insulin glargine offers a more consistent serum level compared to NPH insulin.[26] Insulin glargine had a flat, prolonged action profile, with an onset of action later than NPH. Additionally intersubject variability was lower with insulin glargine than with human NPH insulin.[27] In a comparison study, Porcellati et al., compared once daily insulin glargine given in the evening with multiple daily injections of NPH insulin and continuous subcutaneous insulin infusion. The plasma glucose and insulin concentrations show that compared to NPH insulin, insulin glargine provided less variability in plasma glucose levels, without the glucose dip evident four hours after NPH administration. Plasma insulin levels were steady throughout the night, in contrast to the marked peak and trough associated with NPH insulin.[28,29,30]

Our study evaluated the microdialysis technique for improving glycemic control in type 1 diabetic patients with different basal insulin substitution. The availability of this technique may be helpful for the evaluation of the glucose profile in type 1 diabetic patients treated with different basal insulin supplementation.[7,8,30] This method confirms that basal insulin can be effectively supplied with either two doses of NPH or one dose of glargine. However, glargine achieved a significantly lower HbA1c compared with NPH in patients with type 1 diabetes and glycemic variability measured by *GlucoDay* was also lower with glargine than NPH. The analysis of the *GlucoDay* data demonstrated high inter-individual variability. This type of monitoring supplies extra information on glycemic control that is not predictable from the glycated hemoglobin measurement or from intermittent blood glucose self-monitoring, and is easily used on a routine clinical basis.

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original article

Tuberculosis treatment outcome in a tertiary care setting

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BACKGROUND: The outcome of chemotherapy for pulmonary, extrapulmonary, and disseminated tuberculosis is not well documented, especially in developing countries. This study assessed tuberculosis treatment outcome, cure-to-treatment ratio and mortality among all types of tuberculosis patients in a tertiary care setting in Saudi Arabia.

METHODS: All cases diagnosed and treated for active *Mycobacterium tuberculosis* infection between 1991 and 2000 were included retrospectively. Data collected included type of tuberculosis involvement, treatment outcome, relapse, and co-morbidities.

RESULTS: Over a ten-year period, 535 cases of tuberculosis were diagnosed and treated. Isolated pulmonary tuberculosis was identified in 141 cases (26.4%), extrapulmonary tuberculosis in 339 cases (63.3%), and combined pulmonary and extrapulmonary disseminated involvements in 55 cases (10.3%). Co-morbidities were noted in 277 (52%) patients. Immunosuppression was found in 181 (34%) patients. The cure rate was 82%. The cure-to-treatment ratio was 86% in extrapulmonary tuberculosis and 78% in pulmonary tuberculosis, and 65% in disseminated tuberculosis. Overall mortality was 18%. Disseminated tuberculosis had the highest mortality (34.9%), followed by pulmonary (21.8%), then extrapulmonary tuberculosis (13.6%). Forty-seven percent of all mortalities were directly related to tuberculosis. Relapse was documented in 14 out of 349 patients (4%) who had 24 months of follow up.

CONCLUSION: Despite tertiary care support, complicated tuberculosis carries a high mortality. Earlier diagnosis and complete appropriate chemotherapy are essential for improved outcome.

Treatment outcome serves as a tool to control the quality of tuberculosis treatment provided by the health care system.[1] The global epidemiology of tuberculosis has been shaped in recent decades by HIV/AIDS, urbanization and poverty.[2] In the year 2002, the estimated tuberculosis incidence in the Eastern Mediterranean regiön was 7%. The death rate from tuberculosis, including death in people infected with the human immunodeficiency virus type 1 (HIV-1) was 28 per 100 000 population, the second highest mortality rate after that of Africa.[3] *Mycobacterium tuberculosis* infection in its various forms remains a major cause of high morbidity and mortality among infectious diseases worldwide. Tuberculosis is one of the top ten causes of global mortality.[4] Treatment completion for tuberculosis has been associated with improved patient survival.[5] A successful outcome in active tuberculosis is influenced by establishing an early diagnosis, initiating appropriate therapy, and adhering to and completing a treatment regimen. Relapse was frequent among patients with pulmonary tuberculosis who had received incomplete treatment.[6] As relapse did not occur among patients who have had a full course of modern chemotherapy, abolishing routine follow up was recommended. The rate of tuberculosis relapse is low for those who complete the treatment irrespective of the site of involvement.[7] Data on tuberculosis outcome, mortality, and relapse are limited in immunocompromised patients or patients with co-morbid conditions from developing countries. In this study, we report treatment outcome and mortality and compare the cure, relapse, and tuberculosis-related mortality for all pulmonary, extrapulmonary, and disseminated involvements at a tertiary care center.

METHODS

All cases of *M. tuberculosis* infection between 1991 and 2000 were identified from the databases of the Section of Infectious Diseases, Infection Control, and the Microbiology Laboratory. The outcome of all tuberculosis cases diagnosed and treated at King Faisal Specialist Hospital and Research Center was assessed retrospectively. This 700-bed facility is the main national tertiary care referral center for cancer, cardiac, organ and bone marrow transplantation, and HIV-infected patients. Demographic, clinical, and outcome data were abstracted from medical records using a uniform data collection form. Mortality data were assigned as tuberculosis-related (patients died on treatment due to tuberculosis or its complications) or unrelated (patients died due to medical conditions other than tuberculosis during or after treatment) by a single reviewing investigator. Cases were classified into extrapulmonary tuberculosis where organs other than the lungs were involved by *M. tuberculosis*. If the lungs were also actively involved as evidenced clinically, radiologically, or microbiologically, the condition was considered disseminated tuberculosis. Isolated pulmonary tuberculosis was considered if patients had evidence of tuberculosis involving the lungs only. All treatment courses were based on the guidelines of the National Tuberculosis Program, using four drugs. For pulmonary tuberculosis in immunocompetent patients, duration was for six months. For extrapulmonary tuberculosis in immunocompromised hosts, duration was extended to one year.

Terms used in this report are defined as follows:

Treatment completion: record of treatment course completion was noted.

Defaulters: record of loss of follow up, but no record of treatment completion elsewhere.

Transferred cases: transferred to another center but no treatment results available.

Cure: record of cure after treatment completion, based on clinical, radiological, and microbiological evidence.

Relapse: defined as re-treatment within 24 months after completing the initial first course of tuberculosis chemotherapy due to confirmed persistent disease clinically or microbiologically.

Epi Info Version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA and World Health Organization, Geneva, Switzerland) was used for data entry. Statistical analysis was performed using the Statistica Software Package Version 5.0 (StatSoft, Tulsa, OK). The Student's t test was used to calculate continuous variables, and the chi-square or Fisher's exact test was used for proportions. All reported *P* values are two-tailed and a value of 0.05 was considered significant.

RESULTS

Over the study period, 535 cases of tuberculosis were diagnosed and treated. Isolated pulmonary tuberculosis was identified in 141 cases (26.4%), extrapulmonary tuberculosis in 339 cases (63.3%), and both pulmonary and extrapulmonary disseminated involvements in 55 cases (10.3%). Table 1 summarizes the baseline data of all patients. All patients had microbiological and/or histopathological confirmation of tuberculosis except for 22 patients (4%) who were classified as having tuberculosis based on clinical judgment and a favorable response to tuberculosis chemotherapy. Diagnosis was significantly delayed in patients with extrapulmonary tuberculosis compared with patients with isolated pulmonary tuberculosis (7 weeks versus 4.3 weeks, $P=0.003$). Outcome data are summarized in Table 2. Follow-up, treatment, and outcome data were available for 401 patients (75%). Of the 535 patients, care was transferred to other health care facilities in 57 cases (10.6%) and 77 patients (14.4%) defaulted. Co-morbidities were noted in 277 patients (52%). The commonest was intentional immunosuppression therapy for organ transplantation, autoimmune diseases or neoplasia, which were noted in 181 (65.3%).

The overall cure rate for all tuberculosis cases that had follow-up data and completed treatment was 329/401 (82%). The cure-to-treatment ratio was 79/101 (78%), 222/257 (86%), and 28/43 (65%) in the pulmonary, extrapulmonary, and disseminated tuberculosis cases, respectively. Relapse was noted in 14 of 329 patients (4%) who had 24 months of follow up (pulmonary tuberculosis, 4.7%; extrapulmonary, 3.4%; and disseminated tuberculosis, 6.3%). Overall mortality was 72 of 401 (18%). The mortality rate in pulmonary tuberculosis was 22/101(21.8%), extrapulmonary, 35/257 (13.6%), and disseminated tuberculosis, 15/43 (34.9%). Mortality was directly related to tuberculosis in 34 patients (47%). The distribution of tuberculosis mortality for various forms of tuberculosis is presented in Table 3.

DISCUSSION

Although completion of treatment for active cases of tuberculosis is the most important priority for tuberculosis control programs, reporting treatment success rate, mortality, and relapse should also be highlighted. The National Tuberculosis Program (NTP) targets and sets a cure rate of more than 85% of detected

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Table 1. Baseline data on the study population.

	Pulmonary TB n=141	Extrapulmonary TB n=339	Disseminated TB n=55	Total n=535
Percentage female	59%	47%	58%	51%
Mean age, years (SD)*	51 (20)	45 (19)	44 (20)	46 (20)
Duration of symptoms in weeks (SD)†	4.3 (9.7)	7 (8.8)	5.7 (11)	6.2 (9)
Patients with co-morbidities	89 (63%)	156 (46%)	32 (58%)	277 (52%)

Data are number of patients and percentage unless otherwise noted. *Pulmonary TB patients significantly older (P=0.007) †Extrapulmonary cases significantly slower to diagnose (P=0.003)

Table 2. Tuberculosis outcome in a tertiary care hospital.

	Pulmonary n=141	Extrapulmonary n=339	Disseminated n=55	Total n=535
Transferred	18 (12.8)	36 (10.6)	3 (5.5)	57 (10.6)
Dead	22 (15.6)	35 (10)	15 (27)	72 (13.5)
Cured	79 (56)	222 (65.5)	28 (51)	329 (61.5)
Lost to Follow-up	22 (15.6)	46 (13.6)	9 (16.4)	77 (14.4)

Data are number of patients and percentage.

Table 3. Tuberculosis-related and -unrelated deaths among cases with 24 months of follow up.

	Pulmonary n=101	Extrapulmonary n=257	Disseminated n=43	Total n=401
TB-related	10 (9.9)	15 (5.8)	9 (20.9)	34 (8.5)
Not related	12 (11.9)	20 (7.8)	6 (14)	38 (9.5)
Total mortality	22 (21.8)	35 (13.6)	15 (34.9)	72 (18)

Data are number of patients and percentage.

new cases of sputum smear-positive tuberculosis. The NTP emphasizes curing as many patients as possible to reduce transmission of *M. tuberculosis* infection. A cure rate of at least 85% will decrease immediately the prevalence and the rate of transmission. The incidence will decrease gradually and there will be less acquired drug resistance. This in turn makes future treatment of tuberculosis easier and more affordable. Detecting the rate of defaulters will estimate roughly the threat of spreading resistant strains of mycobacteria.[8,9] In this study, 52 of 196 patients (27%) who were potentially infectious (with pulmonary and disseminated type) had no reportable outcome. The majority of them defaulted treatment. We are reporting rates of cure less than the 85% that is recommended by World Health Organization, even when transferred cases and defaulters were excluded. The cure-to-treatment ratio was 78% in the pulmonary and 65% in the disseminated type of infection.

The overall treatment success rate of all tuberculosis cases diagnosed between 1993 and 1999 from a tertiary care hospital in the western region of our country with a high prevalence of tuberculosis was 69.4% when patients who were lost to follow-up were excluded.[10] Such data are not only reflective of the tuberculosis treatment and control program, but also the competence of the health care system in identifying these cases, instituting appropriate treatment and successfully completing the course of chemotherapy.

The considerably high mortality rate among study cases may be related to the high population of patients with severe co-morbid illnesses in whom the diagnosis was delayed. It indicates the significant impact of the disease in severely ill patients, or those who are requiring corticosteroids. Such settings are associated with high mortality rates and low treatment success rates.[11-14] This hospital has been serving a large population of patients with immunocompromised conditions as a referral hospital, transplantation, hematology/oncology and HIV treatment center. In fact, the study institute has been managing more extrapulmonary tuberculosis since its early days.[12-14] Worldwide, the case-fatality rate of smear-positive pulmonary tuberculosis among persons on treatment is 3.8%.[15] There are limited data reporting treatment completion from the developing countries. The mortality among patients with pulmonary tuberculosis in a teaching hospital in Ghana was associated with increased age and more prolonged symptom duration prior to therapy.[16] In the year 2000, WHO surveillance of tuberculosis treatment in Europe recorded a successful outcome rate of 77%.[17] The tuberculosis treatment outcome in England in a district with high prevalence of disease was 88% for the cure-to-treatment completion ratio, 12% mortality, and a 1% relapse rate among 205 definite cases of pulmonary tuberculosis.[18] Multidrug-resistant tuberculosis (MDR-TB) was inversely associated with a successful outcome.[17] In a referral hospital from Turkey, the tuberculosis treatment success rate between 1997 to 1999 was 71.9%. Failure was encountered mainly among patients with rifampicin resistance and MDR-TB.[19] In our country outcome has never been reported on a large scale, including mortality and relapse. The future tracking of indicators of patient care such as delayed diagnosis and overall tuberculosis-related mortality rate may offer better efficiency in resource utilization, special care for high-risk patients and aid in the conduct of clinical trials.

At tuberculosis care facilities establishment of a management program is recommended as is evaluation of common predictors of outcome at presentation such as age, time from onset of symptoms to diagnosis, chest radiographic findings, culture and susceptibility results, smear status, HIV status, and the presence of associated co-morbid illnesses. Drug resistance proved the most important factor affecting treatment outcome. Success rates in re-treatment of patients with MDR-TB are low.[19] Physicians and other health care providers must devote a great deal of their time and effort to avoiding late diagnosis, start treatment as soon as the clinical suspicion is high, track adherence with medications, defaulters, patients transferred to other local units and make sure that patients with tuberculosis are adequately treated.

The limitation of this study is that it is from a single center and retrospective. The extrapulmonary tuberculosis may have been influenced by the high rate of tuberculous lymphadenitis, comprising around 40% of the cases. The early diagnosis, initiation and completion of appropriate treatment for tuberculosis have to be augmented by raising awareness among care providers.

Data collection, analysis, interpretation, reporting, writing, and drafting the manuscript was done by the authors. There was no outside source of funding or conflict of interest. This work was approved by the IRB (Clinical Research Committee and Research Ethics Committee), (RAC # 2031 001)

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original article

Extreme elevation of the erythrocyte sedimentation rate in children

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BACKGROUND: Extreme elevation the of erythrocyte sedimentation rate (ESR≥100 mm/hour) is usually associated with significant diseases. This study was performed to assess its significance in pediatric patients seen in Aseer Central Hospital.

METHODS: All ESRs performed for children between September 2001 and December 2002 were reviewed. The medical records of those with an ESR≥100 mm/hr (group 1) were reviewed for age, sex, diagnosis, ESR value, hemoglobin (Hgb) value and leukocyte counts. The diagnoses were divided into seven categories: malignancy, connective tissue diseases (CTDs), tropical infections, mild infections, severe infections, renal diseases and miscellaneous. One hundred forty-five patients with an ESR<100 mm/hr (group 2) were randomly selected for comparison.

RESULTS: Of 2540 ESRs, 99 were ≥100 mm/hr (3.9%). There were 54 males and 45 females and the mean age was 72±48.2 months. Infection was the most common cause (49.5%), followed by CTDs (26.3%), malignancy (12.1%) and renal diseases (8.1%). Malignancy was associated with the lowest Hgb value (8.2 g/dL). A comparison between group 1 and group 2 considering each diagnostic category separately showed that group 1 patients with mild infections had significantly higher mean leukocyte counts and that group 1 patients with CTDs had significantly lower Hgb values than group 2 patients with the same diagnoses, but there were no significant differences between the other diagnostic categories.

CONCLUSION: The most common cause of extreme elevation of ESR is infection. This extreme elevation may be used as a sickness index, but not as a screening tool for any disease.

The erythrocyte sedimentation rate (ESR) is one of the oldest commonly used laboratory investigations. It is simple, inexpensive and useful, and its elevation is commonly used as an indicator of certain underlying diseases such as infections, inflammations and malignancies, and to monitor the progress and response to therapy. ESR refers to the rate of fall of red blood cells (RBCs) suspended in plasma. It depends upon the difference in specific gravity between RBCs and plasma, but it is influenced greatly by the extent to which the RBCs form rouleaux, which sediment rapidly. Rouleaux formation and RBC clumping are greatly enhanced by acute-phase reactants in plasma, e.g. fibrinogen, haptoglobin, ceruloplasmin, α1 acid-glycoprotein, and C-reactive protein. It is also increased by immunoglobulins, but is decreased by albumin. RBC intrinsic factors may affect sedimentation; for example, sickle cells and spherocytes sediment slowly, while large RBCs (macrocytes) sediment rapidly. Hyperviscosity, polycythemia and extreme leukocytosis decrease sedimentation while anemia (unopposed by RBC abnormality) enhances sedimentation. Therefore, high ESR is found in conditions that elevate fibrinogen level such as infections, inflammatory diseases, collagen vascular diseases, malignancies (particularly if there is tissue degeneration or metastases), end-stage renal diseases and pregnancy. Hypoalbuminemia (e.g. associated with nephrotic syndrome) elevates the ESR. It is also elevated in conditions that cause immunoglobulinemia, e.g. multiple myeloma. Extreme elevation of ESR (defined as a rate ≥ 100 mm/hour) is often associated with serious diseases.[1,2] This study was performed to address the frequency of extreme elevation of ESR and to ascertain the causes of this extreme elevation in pediatric patients seen at Aseer Central Hospital.

METHODS

Laboratory records of ESR of children up to 13 years of age, performed in Aseer Central Hospital between September 2001 and December 2002, were reviewed.

The medical records of those children whose ESR was ≥100 mm/hr were reviewed and the following variables were obtained : age, sex, diagnosis, ESR value, hemoglobin value (Hgb), and leukocyte (WBC) count.

The patients were divided into seven diagnostic categories: malignancy, connective tissue diseases, tropical infections, mild infections, severe infections, renal diseases and miscellaneous diseases. Infection was considered severe if it was invasive, e.g., septicemia, meningitis, osteomyelitis, septic arthritis, lobar pneumonia, extensive bilateral bacterial bronchopneumonia and pyelonephritis; also, infections associated with hemodynamic instability were considered severe. Statistical analysis was performed using one-way analysis of variance. To make a comparison between patients with ESR≥100 mm/hr (group 1) and those with ESR<100 mm/hr within the same diagnostic categories, a group of 145 patients with ESR <100 mm/hr (group 2) were randomly selected and divided into the same diagnostic categories and the same variables (age, sex, Hgb value and WBC count) were obtained for the analysis. The ESR was performed using a modified Westergren technique using EDTA anticoagulated whole blood. Readings were taken after one-hour incubation.

RESULTS

During the study period, 2540 children had their ESR measured; 99 (3.9%) of them had an ESR of ≥100 mm/hr. There were no statistically significant differences between group 1 and group 2 in sex, age or WBC count (Table 1). The mean Hgb value in group 1 was lower than that in group 2; although this difference was statistically significant, it is of little significance clinically. The mean ESR in those with extreme elevation (group 1) was 118±13 mm/hour (the highest reading was 150 mm/hour); the mean ESR in group 2 (ESR <100 mm/hour) was 30.6±24 mm/hour. The most common cause of extremely high ESR was infection, found in 49 patients (49.5%). The most common infections were lung infections (pneumonia, bronchiectasis and empyema), occurring in 12 patients, followed by meningitis and septic arthritis in 7 patients each; osteomyelitis in 6 patients; malaria in 5 patients; mild viral infections in 4; visceral leishmaniasis in 2 and brucellosis in 1. Connective tissue diseases were the second most common cause of extremely high ESR, found in 26 patients (26.3%). The most common of the connective tissue diseases in this series was acute rheumatic fever, encountered in 19 patients, followed by juvenile rheumatoid arthritis and Kawasaki disease in 2 patients each. Systemic lupus erythematosus occurred in 1 patient only. The third leading cause of extremely high ESR was malignancy, which occurred in 12 patients (12.1%) and included leukemias in 8 patients and lymphoma and neuroblastoma in 2 patients each. The fourth cause of extremely high ESR was renal diseases, occurring in 8 patients (8.1%) and including post-streptococcal glomerulonephritis and nephrotic syndrome in 3 patients each and uremia in 2 patients.

A comparison between the diagnostic categories in patients with ESR≥100 mm/hour (group 1) showed that the mean Hgb value in patients with malignancy was 8.2±3.5 g/dL, which is significantly lower than the mean Hgb value in the other categories (P=0.034). Among patients with infections, those with tropical infections (malaria and leishmaniasis) had a mean Hgb value 8.6±1.9 g/dL, which is significantly lower than in those with other infections. There was no significant difference in the mean WBC count between the various diagnostic groups. Table 2 shows the number and percentage of patients in the various diagnostic categories. Group 1 patients with mild infections had a significantly higher mean WBC count than group 2 patients with mild infections (Table 3). Group 1 patients with connective tissue diseases had a significantly lower mean Hgb value than group 2 patients with connective tissue diseases (Table 3). There were no other significant differences between the two

Table 1. Sex, age, WBC and Hgb values in patients with and without extremely elevated ESR.

	Sex No. (%)	Age in months (Mean±SD)	WBC count (x 10^9/L) (Mean±SD)	Hgb in g/dL (Mean±SD)
Group 1 (ESR ≥100) (n=99)	Male 54 (54.5) Female 45 (45.5)	72±48	12.37±7.1	9.66±2.29
Group 2 (ESR<100) (n=145)	Male 85 (58.6) Female 60 (41.4)	64.5±47	10.93±8.6	11.03±2.26
Statistical significance	χ^2=0.398 NS	t=1.213 NS	t=1.376 NS	t=4.625 Significant

NS=Not statistically significant

Table 2. Disease categories in patients with and without extremely elevated ESR.

	Malignancy No. of patients (%)	Connective tissue diseases No. of patients (%)	Severe infections No. of patients (%)	Mild infections No. of patients (%)	Tropical infections No. of patients (%)	Renal diseases No. of patients (%)	Miscellaneous No. of patients (%)
Group 1 ESR ≥100mm/hr. (n=99)	12 (12.1)	26 (26.3)	31 (31.3)	10 (10.1)	8 (8.1)	8 (8.1)	4 (4)
Group 2 ESR<100mm/hr. (n=145)	10 (6.9)	15 (10.3)	11 (7.6)	64 (44.1)	7 (4.8)	18 (12.4)	20 (13.8)
Statistical significance	χ^2=1.958 NS	χ^2=10.663 Significant	χ^2=23.242 Significant	χ^2=32.256 Significant	χ^2=1.079 NS	χ^2=1.160 NS	χ^2=6.309 NS

NS=Not statistically significant

Table 3. Age, white blood cell (WBC) count and hemoglobin levels in patients with and without extremely elevated ESR within the same diagnostic categories.

	Diagnostic categories						
	Malignancy	**Connective tissue diseases**	**Severe infection**	**Mild Infection**	**Tropical infection**	**Renal diseases**	**Miscellaneous**
	Group 1 (n=12) **Group 2** (n=10)	**Group 1** (n=26) **Group 2** (n=15)	**Group 1** (n=31) **Group 2** (n=11)	**Group 1** (n=10) **Group 2** (n=64)	**Group 1** (n=8) **Group 2** (n=7)	**Group 1** (n=8) **Group 2** (n=18)	**Group 1** (n=4) **Group 2** (n=20)
Age (months)							
Group 1 ESR ≥100	92.8±60	93.2±37.9	55.6±47.3	68.1±49.5	59.6±47	62.4±42.2	55.5±44.2
Group 2 ESR <100	65.8±43.3	88.6±36.8	29.3±20.5	54.6±46.7	70.1±43.6	100.8±48	71.4±49.7
Significance	t=1.191 (NS)	t=0.378 (NS)	t=1.775 (NS)	t=0.844 (NS)	t=0.446 (NS)	t=1.948 (NS)	t=0.592 (NS)
WBC count (x10^9/L)							
Group 1 ESR ≥100	14.2±20	9.6±3.7	14.1±6.7	15.4±5.4	9.1±6.6	13.6±5.4	7.9±2.2
Group 2 ESR <100	12.5±18.2	11.4±5.97	12.3±5.4	10.7±5.3	5.9±2.3	11.4±6.1	11.8±10
Significance	t=0.207 (NS)	t=1.195 (NS)	t=0.801 (NS)	t=2.602 (Significant)	t=1.405 (NS)	t=0.877 (NS)	t=0.763 (NS)
Hemoglobin (g/dL)							
Group 1 ESR ≥100	8.2±3.5	9.6±2.7	10.4±1.6	10.6±1.5	8.6±1.9	8.7±1.9	10.2±1.8
Group 2 ESR <100	9.5±2.6	11.1±1.2	10.9±2.48	11.5±1.79	9.5±2.13	10.4±2.6	11.3±2.7
Significance	t=0.971 (NS)	t=2.031 (Significant)	t=0.766 (NS)	t=1.507 (NS)	t=0.865 (NS)	t=1.655 (NS)	t=0.773 (NS)

NS = not statistically significant

groups.

DISCUSSION

Extreme elevation of ESR ($\geq$100mm/hour) in children is alarming and should be considered a sign of a significant underlying disease. The frequency of this extreme elevation in our pediatric patient population (3.9%) was comparable to that reported previously in other pediatric series (4.9%),[2] and adult series (2.5%,[1] 3%,[3] 4.2%[4]), but lower than that reported from tropical areas (12%[5]). Infection was the most common cause of extreme elevation of ESR, accounting for 51% of the cases, which is similar to the findings in other pediatric series (55.8%[2]), and adult series (33%[4], 44.2%[1], 45.5%[5]). Infection is the leading cause both in series from tropical regions[1,5,6] and from non-tropical regions.[3,4] The most common infection was pulmonary infections, accounting for 24% of all infections in this study, which is similar to the findings in other studies.[2,4-6] The second most common infection was meningitis, accounting for 14% of infections. Although malaria, leishmaniasis and brucellosis are common in our region, they accounted only for five, two and one of the patients with ESR$\geq$100 mm/hour, respectively. Reports from tropical areas[1,5,6] suggest that these common infections are not among the common causes of extreme elevation of ESR. Pulmonary tuberculosis, which is one of the most common causes of pneumonia associated with this extreme elevation in some tropical areas where HIV infection is common,[6] was not encountered in the present study. Connective tissue diseases were the second most common diagnostic category causing extreme elevation of ESR, and rheumatic fever was the most common disease among this category; this is similar to the findings of other studies reporting on children[2] and adults.[1] In areas where both rheumatic fever and brucella arthritis are common, an ESR$\geq$100 mm/hour may favor the diagnosis of rheumatic fever arthritis; this is particularly helpful in patients presenting with arthritis as a sole major feature. Malignancy was the third most common cause of ESR$\geq$100 mm/hour. Although malignancy was reported to be the most common cause in a very early study (58% of cases),[7] subsequent studies have shown this to be the third leading cause.[1,2,4] The present study is in concert with the latter finding; it also suggests that leukemia is the leading neoplastic disease causing extreme elevation of ESR in children as was shown in earlier series.[2] In adults, solid tumors such as bronchogenic carcinoma, hepatocellular carcinoma, gastric carcinoma are the leading neoplastic causes of ESR$\geq$100 mm/hour,[1] and this elevation is often associated with metastasis;[4] however, ESR should not be used as a screening test for malignancy as the sensitivity of an ESR $\geq$ 100 mm/hour for malignancy is low, and at its best ranges from 25% to 49%.[4,5]

Renal failure, nephrotic syndrome and glomerulonephritis are frequent causes of extreme elevation of ESR, and therefore the latter may not be a useful indicator of infections commonly encountered with these diseases (for example, peritonitis and catheter infections). Infections, malignancy, connective tissue diseases and uremia are known to increase fibrinogen level and cause anemia and these in turn may elevate the ESR. However, the mere finding of extreme elevation of ESR should not trigger lists of advanced and invasive investigations searching for some of these diseases, as the clinical scenario at hand should dictate further investigations. In conclusion, extreme elevation of ESR is uncommon in the pediatric age group and is most commonly associated with infection. Extreme elevation of ESR in children may be used as a sickness index, but not as a screening tool for diseases.

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Sonographic fetal weight estimation using femoral length: Honarvar equation

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BACKGROUND: Fetal growth is the result of interactions between various factors and can be estimated by ultrasonic measurements. Fetal femur length is a scale for estimating the fetal weight in individual races because fetal growth patterns differ among different races.

SUBJECTS AND METHODS: This was a prospective study involving 500 pregnant women at 36 weeks of gestational age. Real-time sonography was done to measure the femoral length and then the weight of the fetus was estimated by the Honarvar 2 equation. The correlation between estimated fetal weight (EFW) and real weight was tested by Pearson correlation coefficient and relationships with the age and BMI of the mother, the sex of the neonate and parity were tested by multiple regression.

RESULTS: EFW by the Honarvar 2 equation correlated significantly with the actual birthweight. Therefore, this equation is valid for fetal weight estimation. It also does not depend on the age and BMI of the mother, sex of neonate, or parity.

CONCLUSION: Ethnicity potentially plays an important role in the fetal weight estimation. The Honarvar formula produced the best estimate of the actual birthweight for Iranian fetuses, and its use is recommended.

The birthweight is an important factor in the outcome of a pregnancy. It is well known that prenatal morbidity and mortality increase in abnormal birthweight range fetuses. They also have poor developmental outcomes.[1] In addition, marked birth traumas have been increased in macrosomic infants.[2] The accurate antenatal measurement of fetal weight is very important. It gives useful information for fetal growth assessment, information that could help to decide the time of delivery, the need for specific obstetrical intervention and delivery at an equipped center.[3]

At present, two-dimensional ultrasonography is the most widely accepted method to estimate fetal weight. This method has been used for more than three decades, and is the most extensively studied modality of birthweight estimation.[4] It has good validity in clinical applications.[5]

Most of the fetal weight estimation models have been derived from data from Western populations.[6-9] Ethnicity and secular changes have been known to affect birth weight.[10-12] Thus, birthweight models derived from one ethnic population and applied in another locality, without the validation of clinical applicability, might result in wrong estimations.[13] It has been demonstrated that birthweight standards change over time, and therefore, it is necessary to regularly revalidate a model in a population. Honarvar published a model for ultrasonic fetal weight estimation in Iran. He believes that fetal femoral length illustrates fetal growth accurately.[14] Femoral length was used in a few other studies to determine fetal growth, which was a significant marker.[15-17] The aim of this study was to test the validity of the Honarvar equation using ultrasonic femoral length measurement of Iranian fetuses collected in a Yazd gynecology and obstetric clinic.

SUBJECTS AND METHODS

This was a prospective observational study, conducted in an obstetric clinic, Shahid Sadoughi Hospital, Yazd, Iran. Five hundred pregnant Iranian women were examined at 36 weeks of pregnancy by ultrasonography. The subjects were invited to participate in this study when they attended the antenatal ward. The inclusion criteria were Iranian ethnic origin, singleton pregnancy, 36-weeks pregnancy and regular menstrual cycles before pregnancy. Exclusion criteria were past history of diabetes mellitus, chronic hypertension and previous stillbirth or fetal anomaly, and use of oral contraceptive pills during the last 3 months before pregnancy. Pregnancies that were complicated by congenital abnormalities were excluded from the validation study. Written consent was obtained from the participants and the study protocol was approved by the research committee at Yazd Shahid Sadoughi Medical Sciences University. The ultrasound examinations were specifically arranged for this study and fetal biometric measurements were performed on all subjects according to the Honarvar formula. Fetal weight was estimated according to femoral length (FL) at 36 weeks of pregnancy and compared to the weight of neonates immediately after birth. The neonates were weighed using a digital baby scale with a standard deviation of ±10 g. FL was measured by the O'Brien method[18] (from the proximal to the distal metaphysic), three times and the mean of the measured length taken as the FL. All measurements were done by one gynecologist using real time linear-array and convex sonography with a transducer with 3.5 MHz power.

The Honarvar 2 equation was used to estimate fetal weight according to:

$$\text{EFW (kg)} = 0.042\ \text{FL}^2\text{(cm)} + 0.32\ \text{FL} - 1.36$$
$$\text{SD} \sim \pm 235\text{g}$$

The weights of all neonates were measured immediately after birth and compared with the EFW.

The correlation was tested between the EFW and actual weight according to the sex of the neonate, parity, mother's age and body mass index (BMI) by the Pearson correlation coefficient. The mean estimated and actual fetal weights were compared in boys and girls and they were tested by Student's t test. In addition, both mean weights were compared according to parity (0, 1, 2, 3, ≥ 4), mother's age (15-25, 26-35, ≥36 years) and mother's BMI (≤18.5, 18.51-24.9, 25-29.9, ≥30). Significant relationships were tested by Student's t test. The effect of the sex of the fetus, parity, mother's age and BMI on the predicted fetus weight was tested by multiple linear regression using stepwise technique.

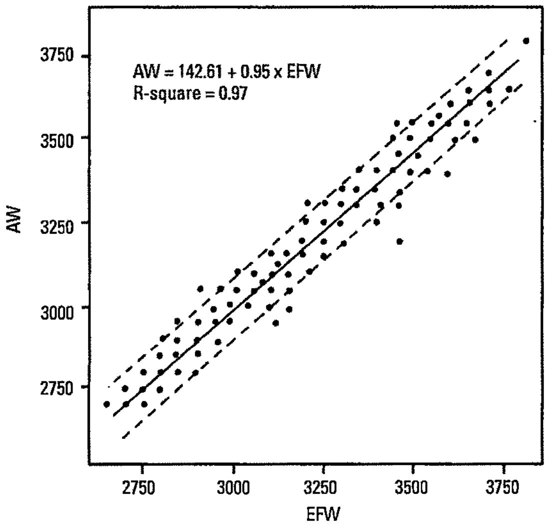

Figure 1. Correlation between estimated fetal weight (EFW) and actual birthweight (AW) (linear regression with 95% prediction interval).

RESULTS

The weight of the fetus was estimated by the Honarvar 2 formula according to FL and then compared with the weight immediately after birth. The mean (±SD) estimated weight was 3188.17 (±414.88) g and the mean weight measured immediately after birth was 3147.62 (±433) g. Estimated fetal weight by the Honarvar 2 equation significantly correlated with actual weight (P=0.001, r=0.983). Therefore this equation is valid for EFW (Figure 1).

The mean of the EFW and actual weight was compared by the gender of fetuses (Table 1) and there were no significant differences between EFW and the actual weight in male and female fetuses, indicating that sex of the fetus has no effect on EFW using the Honarvar equation. In addition, the mean of the EFW and actual weight of the neonate according to parity showed that differences were not significant, which means weight estimated using this formula are not affected by parity (Table 2). The mean of the EFW and actual weight was compared according to the age (Table 3) and BMI of mothers. The mean age was 24 years (15 to 45 years). There were no significant differences between the estimated and actual weights according to age and BMI of mothers, meaning that the age and BMI of the mother have no effect on the estimated weight.

To examine the effect of the sex of fetuses, parity, mother's age and BMI on the predicted fetus weight, a multiple linear regression using stepwise technique was applied. No significant colinearity was found between independent variables in the model so the predictive ability of the estimated fetus weight on the actual fetus weight is independent of other factors. A multiple regression coefficient of 0.95 was obtained in the model. This significant linear association was confirmed by the related scatterplot as seen Figure 1 (P=0.001).

Table 1. Estimated fetal weight and actual birthweight by fetus gender.

Sex	N	Percentage	Mean (±SD) estimated weight	Mean (±SD) actual birth weight
Boy	253	50.6	3190.6±463	3160.8±421.4
Girl	247	49.4	3181.6±400.5	3134.1±408.9

No signficant differences in estimated fetal weight or actual birthweight.

Table 2. Estimated fetal weight and actual birthweight by parity.

Parity	N	Percentage	Mean (±SD) estimated weight	Mean (±SD) actual birth weight
0	158	31.6	3201.4±381.4	3192.8±408.2
1	134	26.8	3141.1±444.9	3066.8±486.6
2	104	20.8	3184.5±438.4	3158.1±41.2
3≤	104	20.8	3022.8±399.2	3172.7±398.7
Total	**500**	**100**	**3188.2±414.9**	**3147.6±433.1**

No signficant differences in estimated fetal weight or actual birthweight.

Table 3. Estimated fetal weight and actual birthweight by mother's age.

Mother's age	N	Percentage	Mean (±SD) estimated weight	Mean (±SD) actual birth weight
15 – 24	229	45.8	3185.6±418.8	3148.5±464.3
25 – 29	129	25.8	3196.7±433.4	3166.2±438.2
30 – 45	142	28.4	3177.4±393.5	3122.3±374.2
Sum	**500**	**100**	**3188.2±414.9**	**3147.6±433**

No signficant differences in estimated fetal weight or actual birthweight.

DISCUSSION

Estimation of fetal birthweight gives useful information about fetal growth, which helps determine the viability of the fetus or its chances of survival as well as the time and type of delivery. The few models used for the estimation of the fetal weight depend on ethnicity and regional differences in growth patterns.[10-12] However, Raman et al believed that ethnicity did not affect growth pattern.[19] Honarvar established a model for Iranian ethnicity, which we validated in the present study. The weight estimated by this equation was significantly near to the actual weight. This model is simple and only requires the FL of the fetus, while others need more than one measure. In addition, FL has been shown to be as accurate as biparietal diameter in estimating gestational age.[21-22] The normal ultrasonic fetal femur length curve of one population is unsuitable and inappropriate for another population.[14] Racial differences are due to genetic factors differences in the environment or social conditions are not relevant.[23]

The results of this study showed that there is no significant relationship between the sex of the neonate and estimated fetal weight. No effect of gender was noted on the growth of FL, therefore, this formula is not affected by the gender of the neonate and determination of the sex of the neonate is not important in assessing uteral growth.[19-20]

No differences in EFW were noted by parity of the mother, which is confirmed by other studies.[19,24,25] However, parity affected the limb length of Indian fetuses. The fetuses of multiparas have limb lengths significantly smaller than the fetuses of primiparas, but the rate of growth was not affected.[26] Neonates of Malaysian, Chinese and Indian multiparas mothers were heavier than those of primiparas mothers.[27]

The age or BMI of mothers showed no effects on EFW, which were tested by others and were not associated with the accuracy of the EFW.[24,25,28] Maternal factors do not alter the accuracy of sonographic fetal weight, so fetal weight prediction provides equally accurate and valid guidelines for determining management decisions in women regardless of maternal factors.[29,30] However, other studies showed that younger and older mothers have lighter babies than mothers in the middle, with an optimal age of 28 years.[23]

In conclusion, this study shows that Honarvar models produced the best estimate of the actual birthweight in Iranian fetuses, which is accurate and simple and only based on femoral length. Knowledge of other variables is unnecessary to estimate fetal weight because there were no significant relationships between EFW and mother's age and BMI, parity and sex of the fetuses. Honarvar et al believes that the EFW according to this model is not accurate for other ethnic populations. Hadlock's equation estimates Iranian neonate weight lower than actual weight while estimated weight according to Ott's protocol is higher than actual weight.[31] So any given ethnic community needs a specific protocol for themselves and ethnicity potentially plays an important role in the fetal body weight estimation, which provides a valid guide for determining management despite maternal factors.

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Abdominal Compartment Syndrome

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The term abdominal compartment syndrome (ACS) describes the clinical manifestations of the pathologic elevation of the intra-abdominal pressure (IAP). When the IAP exceeds 12 mm Hg it is referred to as intra-abdominal hypertension (IAH) while ACS generally sets in at an IAP in excess of 20 mm Hg. This syndrome is most commonly observed in the setting of severe abdominal trauma and in the aftermath of major abdominal operations. ACS affects mainly the respiratory, cardiovascular, renal, gastrointestinal and the central nervous systems. Fundamental to the development of ACS are the obstruction of venous return to the heart via the inferior vena cava and the splinting of the diaphragm due to elevated IAP. Preventing ACS by the identification of patients at risk and early diagnosis is paramount to its successful management. To this end a high index of suspicion is sine qua non. The management of established ACS requires clinical astuteness and decisiveness with a readily available and generous team support. The purpose of this review is to enhance awareness among clinicians about a subtle condition with a devastating impact on morbidity and mortality if undiagnosed.

There are three important considerations to be made in attempting to understand the abdominal compartment syndrome (ACS). Firstly, the abdomen is a conduit of major blood vessels of the body as they course to and from the organs that they supply or drain. Secondly, the peritoneal sac, the anterior abdominal wall and the retroperitoneal space are potential restraints that can passively transmit extrinsic pressure on the vessels and restrict circulation. And thirdly, the gut mucosal barrier, contained in the abdominal compartment, is the biological equivalent of a demilitarized zone between two opponents: the pathogenic commensals in the lumen and the reticuloendothelial system.

The abdominal compartment normally sustains a pressure of about 5 mm Hg, but can be non-pathologically elevated in the obese.[1] Many pathologic conditions can generate sustained pressures in excess of 12 mm Hg, a state referred to as intra-abdominal hypertension (IAH),[1] producing sub-clinical organ dysfunctions (regarded here as prodromes) leading to multiple organ dysfunction syndrome (MODS). Thus, ACS is seen as the end result of a sustained IAH.[1-3]

Historical Milestones

Credit for the first recorded account of an abnormal increase in intra-abdominal pressure (IAP) goes to the French physician Etienne-Jules Marey[4] in 1863. He published a paper titled *"Physiologie Medicale de la Circulation du Sang"* and noted that the effects that respiration produces on the thorax are inversely related to those in the abdomen. Wendt,[4] in 1873, measured the IAP through the rectum and noted that the higher the IAP the less the secretion of urine. That was the first description of organ dysfunction directly attributable to elevated IAH. In rapid succession others championed our understanding of ACS. Oderbrecht[4] in 1875 cannulated the urinary bladder and reported that the IAP is normally positive. In 1890 Heinricius[4] reported that IAP between 27 to 46 cmH_2O (19.8 to 33.8 mm Hg) was uniformly fatal to experimental animals and he attributed his observations to obstruction of ventilation, decreased end-diastolic volume and a low blood pressure.

In the United States, in a luminous paper in 1911, Haven Emerson[5] reported convincing experimental observations. He noted that the contraction of the diaphragm is the main contributor of IAP during inspiration; that hypnosis and muscle paralysis induced by anesthesia with the concomitant loss of muscle tone results in a decrease in IAP; that elevated IAP leads to an increase in peripheral vascular resistance; and that high IAP results in the death of the animal from cardiac failure long before asphyxiation develops.

Sir Heneage Ogilvie[6] in Britain in 1940 described the use of vaseline impregnated canvas or cotton sutured to the edge of the wound as a way of avoiding closing the abdomen under tension. In a similar endeavor, Gross[7] in 1948 described the so-called staged abdominal repair (STAR) operative technique in the closure of the abdomen in the management of large omphaloceles. In 1951, Baggot,[8] an anesthesiologist from Dublin, observed the detrimental effect of IAH on respiratory parameters and noted that forcing distended bowel back into the abdominal cavity of limited volume might kill the patient and he coined the term "acute tension pneumoperitoneum". By 1969 some publications[9,10] advocated leaving the abdomen open in children with omphalocele and gastroschisis. In 1972 it was observed[11] that the application of the Military Anti-Shock Trousers (MAST) resulted in decreased cardiac output and depressed renal function.

The most comprehensive description of ACS is credited to Kron et al.[12] who in 1984 published their observation on IAH and for the first time advocated abdominal re-exploration and decompression as a life-saving intervention, whatever the cause. The first use of the term abdominal compartment syndrome was, however, by Robert Fietsam et al.[13] Other papers[14,15] rapidly appeared about this time, confirming earlier observations and defining this syndrome more clearly.

Epidemiology

The epidemiology of IAH and ACS are intrinsically tied to the level of awareness of these conditions among clinicians and on the population studied; for example, among a trauma population as compared to patients who have undergone damage control surgery. However, studies conducted as recently as in 2006 showed a lack of consensus regarding the definition, functional indications, or management of an open abdomen in the perceptions of Canadian trauma providers despite a high self-reported level of familiarity with ACS.[16,17] In Australia,[18] despite familiarity with the technique of intra-abdominal pressure monitoring and the signs of IAH, ICU registrars lacked sufficient understanding of the retroperitoneal causes of, and the threshold for intervention in ACS. And in the United Kingdom,[19,20] it was observed that fewer patients are diagnosed with ACS in district hospitals than in teaching hospitals and that there was a variable threshold for the diagnosis of the condition as well as disparity in the number of patients who are decompressed suggesting a lack of agreement in the management of this condition.

The point prevalence of IAH and ACS have been estimated at 50.5% and 8.2% from a six-country international European collaboration[21] which showed (in a mixed ICU population) that non-survivors had a significantly higher mean IAP on admission than survivors and that independent predictors of mortality included age, APACHE II score, the type of ICU (odds ratio 2.5 medical vs. surgical) and the presence of liver dysfunction. Studies from Germany[22] and the USA[23] have reported mortality rates of around 60% from ACS in intensive care units.

The World Society for the Abdominal Compartment Syndrome (WSACS)[24] is championing research in and promoting the awareness of this disorder. To standardize terms and definitions, it has just launched the most authoritative textbook[25] on the subject at its recently concluded 3rd congress held in the city of Antwerp, Belgium from March 21-24, 2007.

Etiology and Classification

The WSACS has classified ACS into three categories: primary, secondary and tertiary (recurrent) types. Primary ACS is defined as "a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or radiological intervention".[1] Examples of etiologic factors here include severe blunt and penetrating abdominal trauma,[26-28] ruptured abdominal aortic aneurysm or a leak from an aneurismal repair,[29-31] damage control surgery with packing of the liver,[32,33] primary closure of the abdomen under tension,[34] and pelvic fractures or extraperitoneal hemorrhage.[35-37] Patients who undergo an initial trial of non-operative management for solid organ injuries and who subsequently develop ACS are included in the primary category. Secondary ACS is defined as due to "conditions that do not originate from the abdomino-pelvic region".[1] Examples of causes of secondary ACS include sepsis and capillary leak,[38-40] severe acute pancreatitis (SAP),[41,42] major thermal burns[43-46] and other conditions requiring massive fluid resuscitation.[47-49] Tertiary (recurrent) ACS "refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS".[1,50]

Pathophysiology

Gastrointestinal System

Fundamental to the understanding of the pathophysiology of ACS is the understanding of the concept of abdominal perfusion pressure (APP) in much the same way as cerebral perfusion pressure (CPP) is in relation to raised intracranial pressure. APP is the difference between the mean arterial pressure (MAP) and intra-abdominal pressure (IAP) which is represented mathematically as:

$$APP = MAP - IAP$$

An APP of 50 mm Hg or higher is the optimum resuscitation goal in all critically ill patients.[51]

Splanchnic ischemia (the "first hit") caused by hemorrhage is the initiating event[52,53] leading to neutrophil priming, which promotes local and remote organ injury by several immune-mediated mechanisms[54,55] that include free-radicals like superoxide, enzymes for membrane degradation like elastase, increased CD11b/CD18 expression for endothelial adhesion, elaboration of the chemo-attractant IL-8 to recruit more neutrophils and delayed apoptosis to sustain cytotoxicity.[56] Decompressive laparotomy (DL) as the definitive treatment of ACS brings with it fresh problems (the second hit) to this pathophysiological conundrum. ACS relieved by DL allows a bolus of inflammatory agents to enter the systemic circulation and constitutes an ischaemia-reperfusion injury.[57] Mesenteric lymphatic circulation has been implicated as the conduit for the systemic distribution of proinflammatory cytokines, metabolites of arachidonic acid,[58] complement[59] and bacterial translocation.[60] This has been proposed as the mechanism for remote organ injury, capillary leak and endotoxemia in ACS (Figure 1).[61-63]

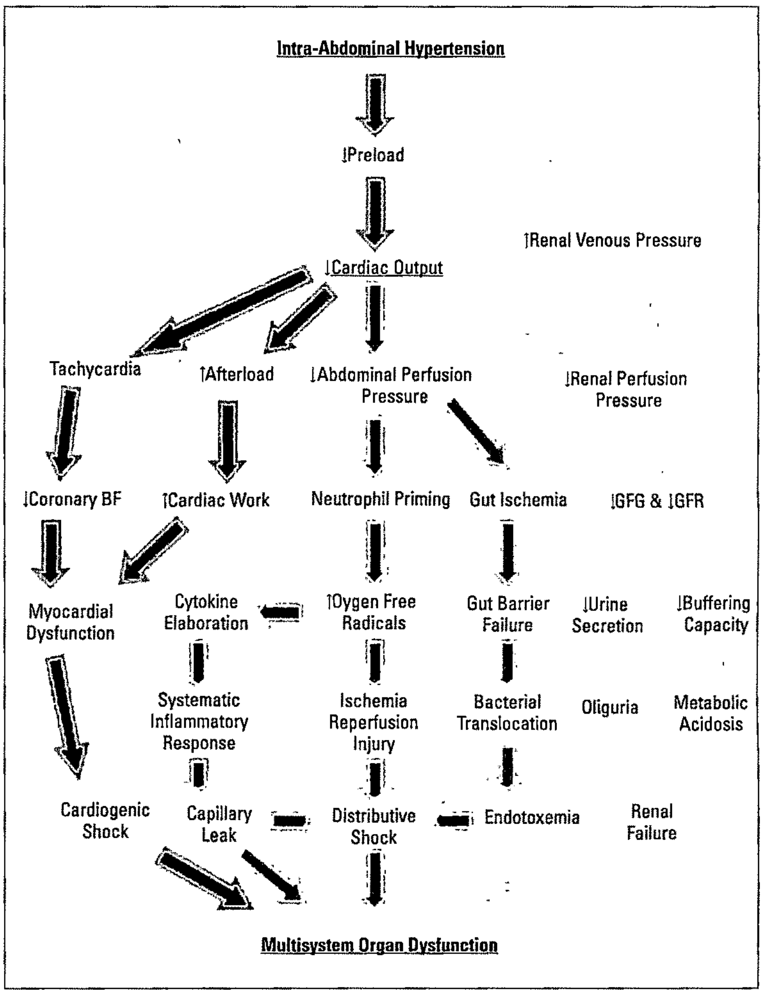

Figure 1. Pathophysiology of intra-abdominal hypertension on the cardiovascular (purple arrows), gastrointestinal (green arrows) and the renal (orange arrows) systems producing multisystem organ dysfunction in abdominal compartment syndrome. SIRS = systemic inflammatory response syndrome, GFG = glomerular filtration gradient, GFR = glomerular filtration rate, BF = blood flow.

Cardiovascular System

IAH affects the cardiovascular system by disturbing preload, myocardial contractility and afterload.[64] Low preload may be due to absolute loss of intravascular volume or relative loss through the compression of the inferior vena cava (IVC) as it traverses the diaphragmatic hiatus. Pooling of blood in the pelvis and the lower extremities constitutes a loss and may be a factor in the pathogenesis of deep venous thrombosis.[65]

The increased intra-thoracic pressure increases pulmonary vascular resistance and decreases right ventricular preload compromising the ability of the thin-walled right ventricle (RV) to effect adequate right ventricular ejection fraction (RVEF) and a consequent decrease in left ventricular end-diastolic volume and diminished left ventricular ejection fraction (LVEF). The resultant low cardiac output (CO) triggers a compensatory tachycardia and a consequent shortened cardiac cycle (at the expense of diastolic time) leading to impaired coronary blood flow. Thus, at the time the heart has to work the hardest, its own blood supply is impaired (Figure 1). The compensatory peripheral vascular resistance due to the low cardiac output together with the compressive effect of IAH on the aorta and its branches contribute towards the low APP.

Respiratory System

Raised IAP is transmitted across the diaphragm producing elevated intra-thoracic pressure, compressive atelectasis, increased alveolar dead space, reduced functional residual capacity, ventilation-perfusion mismatch and hypoxic bronchial artery vasoconstriction. By the same token, the splinting of the diaphragm leads to the need to use the accessory muscles of respiration in the presence of diminished chest wall compliance and so increases the work of breathing. In patients under mechanical ventilation, the decreased dynamic lung and

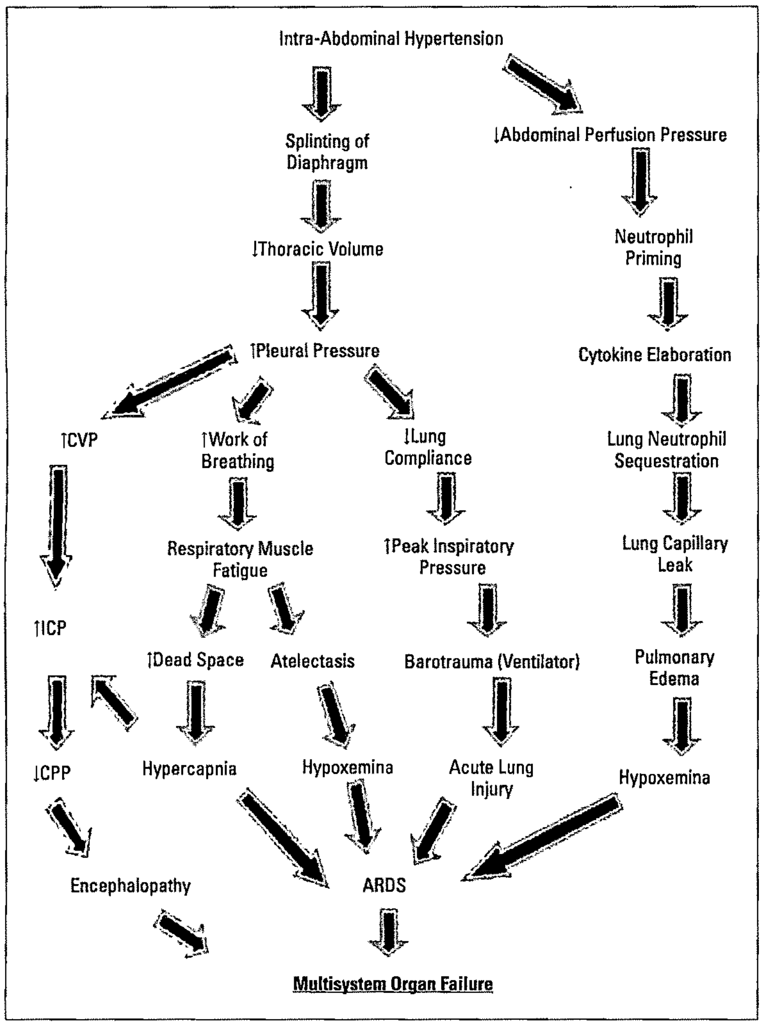

Figure 2. . Pathophysiology of intra-abdominal hypertension on the respiratory (blue arrows) and the central nervous (orange arrows) systems producing multisystem organ dysfunction in abdominal compartment syndrome. CVP = central venous pressure, ICP = intra-cranial pressure, CPP = cerebral perfusion pressure, ARDS = adult respiratory distress syndrome.

chest wall compliances result in elevated peak inspiratory and plateau pressures in attempts by the ventilator to deliver preset tidal volumes (Figure 2).[66]

Central Nervous System

The central venous pressure (CVP) in shock induced by ACS is often elevated due to the high intra-pleural pressure producing a functional obstruction of the jugular veins, resulting in a raised intracranial pressure (ICP). Therefore, the cerebral perfusion pressure is decreased in obedience to the Monroe-Kellie doctrine (Figure 2). The resultant cerebral hypoxia results in encephalopathy and affects vital regulatory centers in the brain, thereby disturbing homeostatic mechanisms.

Joseph et al[68] studied the effects of raising the IAP using pneumoperitoneum on ICP and CPP. They demonstrated that IAH increases ICP and concluded that laparoscopy would be harmful in patients with head injury. Subsequently, reports of the detrimental effects of pneumoperitoneum on ICP[69] and the beneficial effects of DL on ICP[70] appeared confirming the earlier assertions. It has, therefore, been proposed that the monitoring of IAP in patients with head trauma and abdominal trauma be routine.[71,72]

Renal System

The effect of IAH on the renal system is multi-factorial and includes decreases in CO, renal perfusion pressure (RPP), glomerular filtration gradient (GFG), microcirculatory flow, direct compression of the renal cortex, and increased renal venous pressure (RVP).[73] Of these, it appears that increased RVP plays the most significant role in the pathogenesis of IAH-induced renal failure (Figure 1).[74] The reduction of RPP and the reduction in the GFG (the net force acting across the glomerulus) as well as the effects of the hormones vasopressin, renin-angiotensin and aldosterone probably work in concert to produce renal failure in IAH.

The Abdominal Wall

IAH reduces the abdominal wall blood flow by the direct compressive effect. Blood flow to the rectus abdominis muscle is reduced by 60% at an IAP above 10 mm Hg. As collagen deposit and resistance to infection are directly proportional to tissue perfusion and oxygenation, elevated IAP adversely affects wound healing and leads to wound dehiscence.[75]

Diagnosis

ACS has been described as the presence of a tensely distended abdomen, elevated intra-abdominal and peaked airway pressure, inadequate ventilation with hypoxia and hypercarbia, impaired renal function, and a documented improvement of these features after DL.[76] While the virtues of clinical assessment cannot be debated, the detection of IAH by palpation of the abdomen has proved to be insensitive in differentiating IAPs of 10 from 20 mm Hg[77] and serial measurement of the abdominal circumference did not show any correlation with the IAP.[78] Therefore, the identification of patients at risk of developing IAH carries with it the responsibility for a deliberate and diligent monitoring of IAP, especially in patients that are comatosed or intubated.

The abdominal CT scan has a role in identifying ACS in selected patients by the following subtle findings:

- Round-belly sign-Abdominal distention with an increased ratio of anteroposterior-to-transverse abdominal diameter (ratio >0.80; P <0.001);
- Collapse of the vena cava;
- Bowel wall thickening with enhancement;
- Bilateral inguinal herniation.[79]

In the 144 years since the publication of the findings of Etienne-Jules Marey,[4] the techniques of IAP have gone through several modifications. A detailed description of each technique is beyond the scope of this article but those interested can find them in the WSACS textbook.[80] The first method described to find clinical applicability was by Kron et al.[12,81] This method entails instillation of 60 mL of saline through the bladder using an indwelling Foley's catheter. The outlet is then clamped and through a wide-bore needle connected to a manometer or pressure transducer and the pressure is measured. This method has several drawbacks, which include the disruption of the otherwise closed drainage system of the bladder, thereby not safeguarding sterility. The other drawbacks are that the use of needles predisposed healthcare workers to needle-stick injuries and was time-consuming.

Iberti et al[15,82] introduced a modification that had some of the short-comings of the previous method with the advantage that it is simpler, less time-consuming and needed less manipulation. About a decade later, Cheatham and Safcsak[83] introduced a modification that was revised by Malbrain[84] which serves as the current standard for the intra-vesical technique. Using a three-way Foley's catheter, investigators in Australia[85] have shown that a continuous measurement of IAP is possible and of practical advantage in critically ill patients.

Aside from the intra-vesical route, the same principle has been applied in measuring the IAP from catheters inserted into the stomach. A novel method using a fully automated system, the Air-Pouch System (or Spiegelberg System), measures IAP and gastric pH via a nasogastric tube.[86] This system has been tested in an experimental setup with an excellent correlation (r^2=0.99) with direct insufflator pressure.[87] Clinical validation in ICU patients and during laparoscopic surgery has shown excellent correlation (r^2= 0.96) with the standard intra-vesical method.[88] There are on-going efforts to improve on the accuracy and reliability of the current techniques of IAP measurement using piezo-resistive techniques that are showing promising results.[89]

Other routes have been described for the measurement of IAP using the foregoing principle, but none of these have found widespread clinical use. These are the rectum,[90] the uterus[91] and the inferior vena cava (IVC).[92] The problem with the rectal route is that residual faecal matter may block the catheter tip and give an erroneous reading and nursing staff have an aversion for this route. The uterine method has a distinct disadvantage in that it can only be used in females and may be resisted by virgins. The other disadvantage is that it carries the risk of introducing infection and cannot be used in patients with uterine bleeding. The IVC route employs the placement of a central venous catheter through either the SVC or through the femoral veins and is guided into place within the abdominal compartment. The disadvantage of the IVC route is the risk of catheter-related infections and the technical difficulty in the initial insertion.

Management

A subset of ACS can be prevented and to this end, there is no substitute for clinical astuteness, sound judgment and good operative technique. Early goal-directed therapy using the APP in critically-ill or traumatized patients during the resuscitation phase may avert the dangers of over-enthusiastic fluid resuscitation. Confining DCS to the shortest time possible to give opportunity to correct acidosis, hypothermia and coagulopathy—the so-called deadly triad of ACS—is appropriate. Gentle handling of tissue intra-operatively and the avoidance of primary closure of the abdomen under tension are the defining qualities and the hallmarks of good surgical handicraft. It is generally advocated that when the abdominal contents can be viewed protruding above the wound margin when looking across the table at the level of the anterior abdominal wall, temporary abdominal closure (TAC) is the option of choice.[93,94]

Burch et al[95] proposed a four-category grading system for IAH as follows:

Grade I	10-15 cm H_2O (7.5-11 mm Hg);
Grade II	15-25 cm H_2O (11-18 mm Hg);
Grade III	25-35 cm H_2O (18-25 mm Hg); and
Grade IV	>35 cm H_2O (>25 mm Hg).

The authors advocated conservative management for grades I and II and DL for grades III and IV. At first glance, this is useful and practical but, in reality, many surgeons are skeptical about the whole concept of IAH and ACS and would not readily take a patient with, say severe pancreatitis with an IAP of 25 mm Hg, from the ICU to the OR for a DL. This is where the problem lies: the decision to subject a critically ill medical patient with hemodynamic instability (somebody else's headache!) to the additional hazards of the trauma of surgery and general anaesthesia. On the contrary, many published papers show ample evidence that such intervention results in substantial benefit to the patient with improved survival and diminished morbidity.[41,96-100]

There are critically ill patients with IAH and ACS in whom a trial of conservative (medical) management would be appropriate. This may wholly, or in part, be due to four reasons: DL is associated with a less than perfect survival outcome (38-71%);[101] the complications and the cost of management of patients with TAC may be prohibitively high; there are subsets of patients in whom DL may not be necessary; and consent for operation may have been withheld.[102]

The evidence for conservative management is limited by the lack of randomized studies. Therefore, a lot of what is published is based on limited experience and anecdotal reports. Massive distension of the abdomen by postoperative ileus or intra-abdominal pathology may contribute significantly to IAH for which correction of underlying etiologic factors like electrolyte imbalance or the use of prokinetic drugs like erythromycin, metoclopramide, neostigmine, insertion of nasogastric and rectal tubes or colonoscopic decompression may be accompanied by a reduction of IAP. Faecal impaction and intractable constipation may respond to suppositories, enemas or manual disimpaction. In patients under mechanical ventilation, the use of neuromuscular blockade may be a temporizing measure by paralyzing the muscles of the abdominal wall and considerably lowering the IAP. Diuretics and dialysis might help in removing excess interstitial fluid that has contributed to visceral edema in cases where massive fluid requirement for resuscitation led to IAH and ACS such as in burns and SAP. Tapping of a massive ascites may be rewarded with an immediate reduction in IAP, but it is also in these patients with liver failure that the coagulopathy may contraindicate DL.[102]

Where operative intervention is indicated in the treatment of ACS, the operative technique involves opening the abdomen, managing the open abdomen and closing it. The abdomen may be opened for damage-control surgery where the operation is abbreviated and focuses on life-threatening problems like bleeding or it may be planned to release tension in the abdomen such as will be caused by SAP. Prior to this procedure, however, serious complications of reperfusion injury must be anticipated and planned for. A 'decompression cocktail' made of one liter of normal saline, sodium bicarbonate and 50 g of mannitol is administered. This is aimed to increase the circulatory volume, to neutralize a large amount of acidic metabolites from the mesenteric vascular bed and to enhance diuresis to prevent acute tubular necrosis. This is then followed by a temporary abdominal closure which is aimed at ensuring the IAP is not raised by a primary fascial closure (PFC) and to permit easy access to the contents of the abdomen after resuscitation of the patient.[103] Managing the open abdomen is froth with many problems that include sepsis and negative nitrogen balance from loss of fluid from the wound.

Four methods TAC have been described: towel clip closure, Bogota bag closure, mesh closure, and vacuum-assisted wound closure.[104] The towel clip closure method is the cheapest and easiest method and entails using a series of towel clips to hold the edge of the skin at distances 2 to 3 cm apart after hemorrhage has been controlled. The Bogota bag uses a split infusion bag sutured to the edge of the wound to cover the viscera. Mesh closure employs absorbable meshes on the fascial edges with the omentum, if present, interposed between the mesh and the bowels to minimize the risk of fistula formation. The vacuum-assisted technique involves placing a fenestrated non-adherent plastic sheet inside the abdomen extending bilaterally under the anterior abdominal wall followed by a layer of polyurethane sponge that is cut to size and sutured to the edge of the wound incorporating fenestrated tubes connected to vacuum. These are covered with a final air-tight adhesive film.[105,106]

Closure of the open abdomen is planned when edema has subsided and PFC is feasible. Gradual wound closure is attempted using interrupted transverse sutures on the superior and inferior edges of the incision.[104] The technique of component separation[107] is helpful to achieve PFC and involves the partial separation of the muscles of the anterior abdominal wall at the level of their aponeuroses on the abdominal recti in a vertical direction while preserving the neurovascular bundles. A new technique was reported from Sweden using vacuum-assisted closure and gradual shortening of non-absorbable meshes sutured to the wound edges with good results.[107] The use of tissue expanders to aid in PFC is known as well as the use of pedicle or free latissimus dorsi flaps to reconstruct the abdominal wall.[108]

Finally, we must not forget the courageous, lone surgeon working in austere parts of the world without devices for vacuum-assisted wound closure or who may not be familiar with using them. The use of a skin only closure may be a safe and wise option in the aftermath of DCS under such circumstances. The incisional hernia thus created can be repaired at a later date and would amount to an acceptable trade-off for the patient to end up with a temporary disability (hernia) than to risk death by ACS.

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Hepatitis C virus infections reported in Saudi Arabia over 11 years of surveillance

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Hepatitis C virus (HCV) infection is an important public health problem worldwide.[1] As of June 1999, the World Health Organization (WHO) estimated that 169.7 million persons (3% of the world's population) were chronically infected with HCV globally and that 3 to 4 million persons are newly infected each year.[2] The prevalence rate was estimated to be 5.3% in Africa (31.9 million cases), 4.6% in the Eastern Mediterranean region (21.3 million cases), 3.9% in the West Pacific region (62.2 million cases), 2.15% in Southeast Asia (32.3 million cases), 1.7% in the Americas (13.1 million cases), and 1.03% in Europe (8.9 million cases).[1] Data on the prevalence of HCV infection in Saudi Arabia is limited. The objective of this study was to describe the number of HCV infections reported in Saudi Arabia during 11 years of surveillance from January 1995 through December 2005.

METHODS

Saudi Arabia occupies most of the Arabian Peninsula with an area of about 2 240 000 sq km. It comprises 13 administrative provinces, namely, Makkah province (which includes the holy city of Makkah, Jeddah and Tayef), Madinah province (which includes the holy city of Madinah), Riyadh province (which includes the capital city, Riyadh), the Eastern province (which includes Dammam, Ahsa, and Hafr Albaten), Asir province (which includes Abha and Bisha), Jouf province (which includes Jouf and Qerayyat), Hudud Shamaliyah (North Borders) province (which includes Arar), and Baha, Jizan, Najran, Hail, Qassim, and Tabook provinces. The latest census conducted in Saudi Arabia in 2004 indicated that the total population was 22 673 538, of whom, 16 529 302 (72.9%) subjects were Saudis. Approximately, 40.8% of the population is below 15 years. 56.1% are 15 to 64 years, and 3.1% are above 64 years of age. The population annual growth rate is 3.3%. The infant mortality rate is 19.1 per 1000 live births and the maternal mortality rate is 1.8 per 10,000 live births. The total life expectancy at birth is 71.4 years.

HCV infection and other causes of acute or chronic viral hepatitis have been notifiable in Saudi Arabia since 1990. Ministry of Health officials rely on healthcare providers, laboratories, and other public health personnel to report the occurrence of these infections to the Department of Preventive Medicine in the Central Ministry of Health office in Riyadh, where all surveillance data are compiled. HCV infection during the study period was identified by detection of antibodies to HCV (anti-HCV) by enzyme-linked immunosorbent assays (ELISA) and the confirmatory recombinant immunoblot analyses (RIBA). Indications for testing for anti-HCV included clinical suspicion and routine screening of blood and organ donors, contacts of HCV-infected patients, prisoners, intravenous drug users, patients with other sexually transmitted infections, and expatriates pre-employment.

RESULTS

From January 1995 through December 2005, 24 948 cases with HCV infection were reported to the Ministry of Health, of whom 19 185 (76.9%) cases were Saudis. The number of cases by regions is shown in Table 1. The number of HCV infections by region ranged from 33 to 9186 cases with a mean of 1247 cases per region. Figure 1 shows the number of HCV cases by year. Figure 2 shows the number of cases by age groups. The mean size of the pediatric (children <15 years of age) and adult (subjects ≥15 years of age) population during the study period was 8 186 369 and 11 878 260 individuals, respectively. The total number of HCV cases reported among children was 998 cases and that among adults was 23 950 cases.

DISCUSSION

In 1989, HCV was first identified and found to be responsible for most transfusion-associated non-A non-B viral hepatitis.[3,4] Before HCV identification, the major

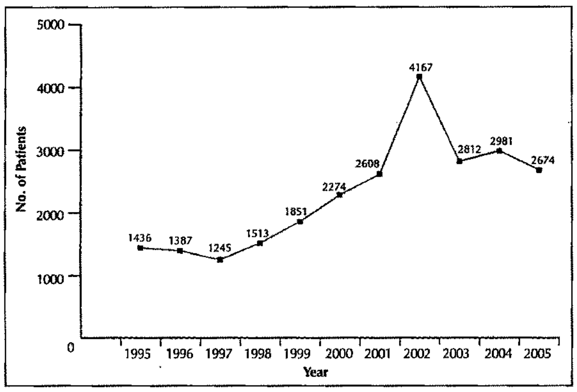

Figure 1. Number of cases of hepatitis C virus infection by year.

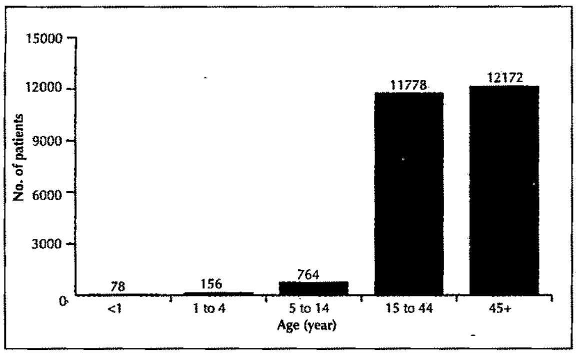

Figure 2. Number of cases of hepatitis C virus infection by age group.

Table 1. Number of subjects with antibodies to hepatitis C virus per 100 000 population by regions in Saudi Arabia (1995-2005).

Region	No. of reported cases	Mean population during the surveillance period
Baha	1268	393 327
Jeddah	9186	2 866 113
Najran	734	356 250
East	3522	1 824 952
Qunfoda	102	55 725
Makkah	2022	1 483 258
Riyadh	4159	4 538 346
Qassim	812	890 625
Bisha	218	288 321
Tabook	389	575 000
Madina	808	1 283 251
Jouf	112	205 882
Asir	568	1 297 311
Ahsa	351	940 217
Qerayyat	33	113 393
Hail	143	487 778
North Borders	78	270 808
Tayef	221	883 186
Hafr Albaten	62	280 727
Jizan	160	1 030 159
Total	**24 948**	**20 064 629**

causes of HCV infection worldwide were the use of unscreened blood transfusions, and re-use of needles and syringes that were not adequately sterilized. Screening of blood and organ donors for HCV since 1990 has virtually eliminated the spread of HCV by these routes. Consequently, sharing contaminated needles has become the most common mode of transmission of this infection.[1] Sexual and perinatal transmission may also occur, although less frequently.[5-7] Infection via other modes of transmission such as ear and body piercing, circumcision, tattooing, and cupping (Hijama) can occur if inadequately sterilized equipment is used.[2]

The prevalence of anti-HCV in some neighboring and other Islamic countries was reported as follows: Algeria, 0.2%, Egypt, 18.1%, Indonesia, 2.1%, Iraq, 0.5%, Jordan, 2.1%, Kuwait, 3.3%, Libya, 7.9%, Malaysia, 3.0%, Mauritania, 1.1%, Morocco, 1.1%, Oman, 0.9%, Pakistan, 2.4%, Qatar, 2.8%, Somalia, 0.9%, Sudan, 3.2%, Tunisia, 0.7%, Turkey, 1.5%, United Arab Emirates, 0.8%, Palestine, 2.2%, and Yemen, 2.6%.[1] The prevalence of HCV in Saudi Arabia and the aforementioned countries is similar to the prevalence reported in industrialized countries.[1] One notable exception is Egypt, in which the prevalence is known to be exceptionally high (up to 40% in some parts of Egypt), probably because of the use of non-disposable, non-sterilized syringes to administer tartar emetic in mass treatment campaigns to control schistosomiasis in the 1960s through 1980s.[8-12]

Previous studies in Saudi Arabia indicated that the anti-HCV prevalence was 0.4% to 1.7% for adults and 0.1% for children.[13-16] For instance, a study in Jeddah among 528 blood donors showed an anti-HCV prevalence of 1.7%.[13] In a large study among 557 813 Saudi subjects of all ages in Riyadh province, the anti-HCV prevalence was 1.1% for adults and 0.1% for children.[14] A study among 24 173 blood donors in Riyadh province over a three-year period from January 2000 to December 2002 showed an anti-HCV prevalence of

0.4%.[15] A recent study among 13 443 blood donors in the Eastern province of Saudi Arabia showed a decline in the prevalence of anti-HCV from 1.04% in 1998 to 0.59% in 2001.[16] In the current study, the number of HCV infections reported in different regions of Saudi Arabia ranged from 33 to 9186 infections with a mean of 1247 infections per region. When expressed per population, these figures translate to a range of 0.016% to 0.322% and a mean of 0.124%. The number of infections reported among adults was 23 950 infections (0.202%) and that among children was 998 infections (0.012%). These figures do not necessarily reflect the actual prevalence of HCV because of the nature of the study design. The relatively low number of reported cases in this study was most likely due to underreporting. The number of cases slightly and steadily rose from 1998 to 2002 perhaps owing to improved reporting and/or population growth estimated to be 3.3% annually. From 2003 to 2005, the number of annually reported cases seemed to have plateaued (Figure 1).

In this study, the number of HCV infections reported among children (0.012%) was much lower than that among adults (0.202%). This suggests that perinatal and childhood transmission is not a major mode of infection. On the other hand, the predominance of this infection in adults suggests that the other modes of transmission such as unscreened blood transfusion before 1990 and intravenous drug use are the main modes of infection in Saudi Arabia. Substance abuse is an increasing problem in Saudi Arabia as it is in the rest of the world.[17-21] Substances abused include injectable drugs such as heroin and cocaine and noninjectable drugs such as cannabis and amphetamine-type stimulants. The estimated annual prevalence of substance abuse in Saudi Arabia in 2000 as percentage of the population aged 15 and above was 0.01% for heroin and 0.002% for amphetamine.[17] The number of drug abusers annually admitted to detoxification centers in Riyadh, Jeddah, Dammam, and Qassim from 1996 through 2001 ranged from 4740 to 6650 patients with an average annual increment of 5.1% (unpublished data). The prevalence of hepatitis C virus infection among 799 drug abusers from a voluntary detoxification unit in Jeddah was reported to be 69%.[18] Thus, substance abuse seems to be a potential major risk factor for the spread of HCV among adults in Saudi Arabia.

The prevalence of HCV infection is lower than the prevalence of hepatitis B virus (HBV) in Saudi Arabia. A recent study showed that the prevalence of HBV infection in Saudi Arabia was on average 0.15% with wide variations between various regions ranging from 0.03% to 0.72%.[22] In that study, the prevalence of HBV among children was 0.05% and that among adults was 0.22%.

Since there is as yet no vaccine to prevent HCV infection, the strategy to prevent this infection in Saudi Arabia focuses mainly on health education, routine screening of blood and organ donors and high-risk subjects such as household and sexual contacts of HCV patients, hemodialysis patients, patients requiring recurrent blood transfusion, intravenous drug users, and patients with other sexually transmitted infections. Additionally, implementation and maintenance of proper infection control practice in health care settings, including standard precautions and proper sterilization of surgical and dental equipment, and good hygienic practice in barbershops and traditional therapy settings such as wet cupping (Hijama) are emphasized in Saudi Arabia.

This study has several limitations. The fact that the study was not a cross-sectional survey but rather a passive reporting of anti-HCV positive cases to the Ministry of Health obviously carried a risk of under- or perhaps over-estimation of the actual magnitude of HCV infection in Saudi Arabia. On the one hand, routine testing of low-risk groups (such as blood or organ donors and expatriates pre-employment) may underestimate the prevalence. On the other hand, testing high-risk groups (such as drug abusers, prisoners, contacts of HCV-infected patients, patients with other sexually transmitted infections) may overestimate the actual prevalence. Another limitation is that information (liver function, cirrhosis, hepatocellular carcinoma) was not reported to the Ministry of Health as this was not part of the notification information mandated by the Ministry of Health. Further, different screening and confirmatory assays were used by different health sectors (the Ministry of Health, the Universities, the National Guard, the Armed Forces, King Faisal Specialist, and the private hospitals).

In conclusion, the incidence of HCV infection in Saudi Arabia is low. In the absence of an HCV vaccine, efforts to prevent the spread of this infection should focus on ensuring safe blood, blood products, and organs for transplantation, ensuring safe use of syringes, needles, sharps, and other equipment used for medical or traditional percutaneous interventions, implementation and maintenance of proper infection control practice in health care settings; and health education particularly targeting high risk groups.

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brief report

Acid resistance of *Salmonella* isolated from animals, food and wastewater in Tunisia

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Salmonella are important foodborne pathogens that infect a variety of hosts and cause a broad spectrum of diseases. During the past few decades, there has been an increase in salmonellosis worldwide. This can largely be attributed to an increase in transmission of broad host-range organisms to humans from infected food and water.[1] However, it is well demonstrated that *Salmonella* can disseminate and survive in various environmental niches for long periods of time. They are pervasive in nature and may contaminate animals, vegetables, water and especially food during its production and distribution.[2]

The spread and dissemination of these enteric pathogens were accompanied by an important increase in resistance to antibiotics all over the world.[3,4] Therefore, these bacteria are developing a cross-resistance to antibiotics often used in therapy or as additives.[5-7] The occurrence of multiple-antibiotic-resistant *Salmonella* was reported in many developed and non-developed countries and continues to cause major health problems.[8-12] Therefore, the use of antibiotics must be restricted to reduce the selection and spread of multi-resistant strains. This urgent need to replace antibiotics has prompted researchers to try to find other alternatives. Consequently, many compounds and chemicals, such as organic acids, were tested for their antimicrobial activities.

Organic acids have long been used both for preserving foods and in livestock production for disease prevention or as growth-promoting feed additives.[13-19] It has thus been demonstrated that organic acids have an antimicrobial activity which is pH dependent.[13] *Salmonella*, as enteric pathogens, encounter a low pH value in the environment, especially during its transit in the host. These bacteria must face this barrier to replicate and proliferate in the hosts. The study of acid resistance in previous research showed that some strains of *E. coli* are able to survive at very low pH values, but stop growing at pH values less than 4.4.[20-22]

This study was undertaken to determine if ten isolates of *Salmonella* could grow on nutrient broth acidified by acids commonly present in foods or used as acidulants. It was also of interest to see whether acid adaptation enhanced the survival and growth of these strains upon subsequent exposure to a low pH environment.

MATERIAL AND METHODS

Strains of *Salmonella* used in this study are described in Table 1. These strains were isolated from foods, wastewater and animals. Bacteria were routinely incubated in nutrient broth (NB) (Pronadisa, Spain) at 37°C overnight with shaking.

Salmonella isolates were assayed for susceptibility to eight different antibacterial agents by the disc diffusion method. All antibiotic discs used were supplied by Biomérieux (France). The respective quantities (μg/disc) of these compounds were as follows: ampicillin (AMP) (10); tetracycline (TET) (30); gentamicin (GEN) (10); nalidixic acid (NAL) (30); chloramphenicol (CHL) (30); amikacin (AMK) (30); neomycin (NEO) (30); streptomycin (STR) (10). The results were interpreted in accordance with the Clinical Laboratory and Standard Institute (CLSI).

All isolates of *Salmonella* were tested for acid resistance. A fresh overnight culture was used to inoculate 50 mL (OD_{600}=0.05) of the NB medium preadjusted with the appropriate acid to the desired pH, then incubated at 37°C with shaking. The optical density and pH of the medium were periodically measured. The pH of the samples were determined with a pH meter (*HANNA* Instruments pH 209) before and after inoculation and during the measurement time (pH 2.5, 3, 3.5, 4, 4.5, 5 and 7 were tested). For all of the acids, concentrations of both 1% and 10% were tested. The bacterial population was determined by plating on NB agar plates 0.1 mL of appropriately diluted cultures which were then incubated at 37°C for 24 hours.

Table 1. Resistance profiles of *Salmonella* isolates

Salmonella serovars	Source	Resistance profile
S. enteritidis	Poultry	TET, STR
S. mbandaka	Meat	TET, AMP, STR
S. lindenburg	Milk	TET, AMP, STR
S. nikolaifleet	Wastewater	TET, AMP, STR
S. cerro	Merguez*	TET, STR
S. montevideo	Wastewater	TET, AMP, NEO
S. hadar	Poultry	TET, AMP, NEO, GEN, STR
S. braenderup	Milk	TET, AMP, STR
S. zanzibar	Wastewater	TET, NAL
S. newport	Wastewater	TET

* A Tunisian food prepared with meat.

RESULTS

In this study, eight antibiotics were tested: ampicillin, tetracycline, gentamicin, nalidixic acid, chloramphenicol, amikacin, neomycin and streptomycin. The findings obtained showed a greater resistance of all non-typhoidic *Salmonella* serotypes isolated from food, animals and water. Tetracycline was the only antibiotic that had no effect on any of the isolates tested. Ampicillin and streptomycin followed in lack of effect. On the other hand, amikacin, chloramphenicol, gentamicin and nalidixic acid were the most active against these isolates. Therefore, in the *Salmonella* population tested, *Salmonella hadar* (isolated from poultry) showed the highest rates of resistance (five resistant) and *Salmonella newport* the lowest (one resistant) (Table 1).

The results showed that the antimicrobial activity of all acids increase as their concentrations increase. For periodic and acetic acids, a concentration of 1% was capable of reducing the number of colony-forming units by a factor of ten, whereas the same concentration of hydrochloric and citric acid reduced this number only by a factor of five. Figure 1 shows the growth kinetics of *Salmonella hadar* when incubated in an NB medium adjusted with the appropriate acid as an example of the responses of the other isolates tested.

However, the results also showed that the minimum pH for growing of all *Salmonella* tested was dependant on the type of acid used. Therefore, the pH was 3 when using citric acid or hydrochloric acid as acidulants and 4.3 when using periodic or acetic acids. Lag time was similar as well for citric and hydrochloric acids. Moreover, acetic and periodic acids were significantly more inhibitory than both citric acid and hydrochloric acid towards all of the isolates tested.

Figure 2 illustrates the growth kinetics of the ten isolates of *Salmonella* in an NB medium with citric acid added at a concentration of 10%. Therefore, except for *Salmonella hadar* which has a pH minimum for growth of about 3, all other isolates have a minimum of about 3.5. In addition, according to Figure 1, an increase in pH from 3.5 to 7 decreases the lag time of all *Salmonella* isolates. This decrease was serotype dependant; however, *S. hadar* showed the least lag time. For *S. enteritidis*, its lag time at pH 3.5 was different from all other isolates.

DISCUSSION

For years, antibiotics have been used in different fields such as medicine, agriculture and the food industry. However, the situation has changed in recent years due to the emergence of bacterial resistance and the decreased effectiveness of antibiotics.[8,9,10,11,23] In Tunisia, few studies have been addressed the antibiotic resistance of *Salmonella* and its evolution. Our results show that the resistance profiles of all serotypes tested are very similar (Table 1). Tetracycline and ampicillin do not show any effect on the isolates. These antibiotics have been the most commonly used and therefore the very frequent occurrence of resistance among *Salmonella* is probably a consequence of this. Although this problem is well documented worldwide, the situation in Tunisia will become more dangerous in the near future.[10,12,23] Abusive use of these molecules in fields such as agriculture, medicine and industry must be limited. Antibiotics must be used only when necessary, and

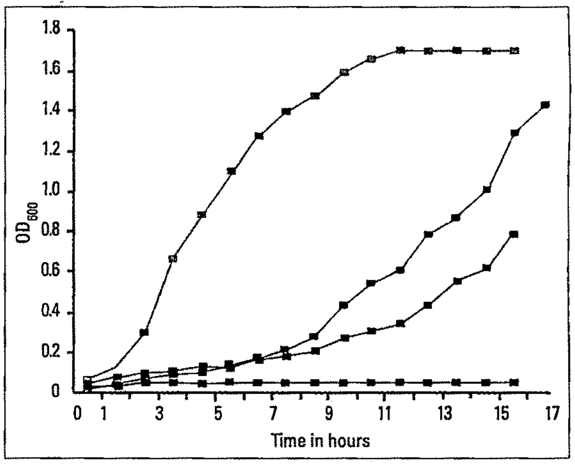

Figure 1. Response of *Salmonella hadar*, incubated in an NB medium with acetic acid (■), hydrochloric acid (■), citric acid (■) at the pH 3.5. All acids were tested at a concentration of 1%. For a control growth curve, *Salmonella hadar* was incubated in an NB medium pH 7 (■) (OD = optical density).

the consumption of antibiotics for purposes other than the treatment of infectious diseases must be avoided as much as possible.[24] Alternatives that are cheap, readily available and have few effects must be substituted.

The majority of treatments used in Tunisia to eradicate pathogens from poultry contain chlorine and present a certain number of disadvantages. However, unlike chlorine, organic acids were recognized as safe for the environment and are generally used as preservatives in food. In this study, the efficiency of organic acids towards these pathogens was tested. Acetic and periodic acids showed great effectiveness on *Salmonella* tested at a concentration of 1% and pH 4. It is well known that organic acids have important antibacterial capacity and no negative effect on the environment.[13] These molecules are thus generally used as food preserving additives.[12,14,15,17,18] At the same concentration and pH, citric acid and hydrochloric acid increase the doubling time of all serotypes tested without affecting their growth and survival. The killing effect of the acids used increased in the following way: citric acid < hydrochloric acid < acetic acid < periodic acid. The results showed that the situation would be clinically worse for the following reasons: First, acid tolerance is a contributing factor in the intracellular survival and virulence of *Salmonella*. Secondly, some isolates have also demonstrated high levels of resistance. In fact, Wain et al have suggested the existence of a relationship between virulence and drug resistance.[25] Therefore, it should be stressed that pathogens have shown both high levels of drug resistance and also acid resistance, especially *Salmonella hadar*, which has the highest antibiotic and acid resistance. This link between acid and antibiotic resistance could have significant implications for the food industry and needs to be further investigated in foodborne pathogens in a real food-processing situation. The acid tolerance response provides cross-protection to heat, osmotic, and oxidative challenges.[26] This work could help to assess the risk of stressed-adapted bacteria and alert public health professionals and inspection authorities.

We are grateful to Mr. Ben Aissa Ridha (Institue Pasteur de Tunis) for providing strains of Salmonella. *This work was supported by the Ministère de l'Enseignement Supérieur, Tunisie.*

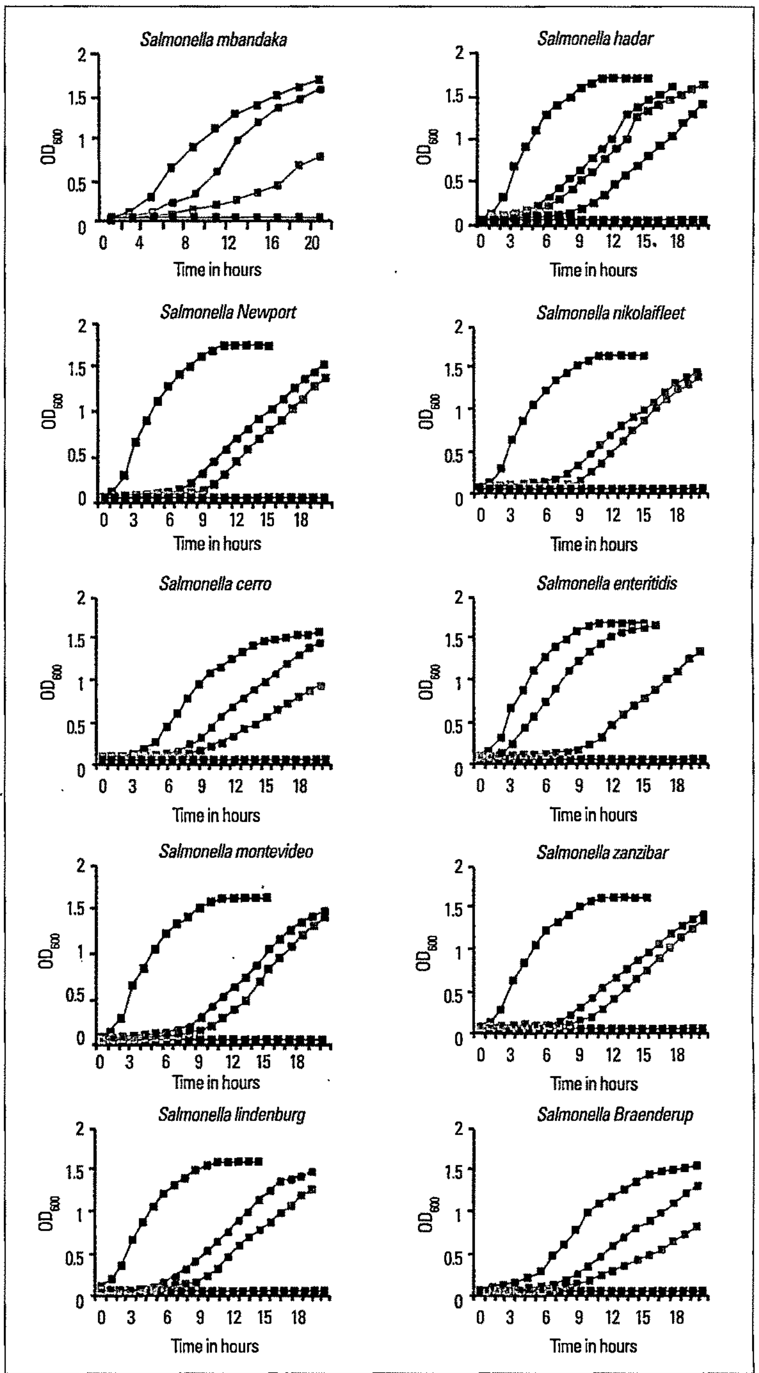

Figure 2. *Salmonella* isolates incubated in an NB medium adjusted by citric acid (1%) at range of pH 7 (■), pH 4 (■), pH3.5 (■), pH 3 (■) and pH 2.5 (■). (OD = optical density).

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case report

A retroperitoneal bronchogenic cyst successfully treated by laparoscopic surgery

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Bronchogenic cysts are rare benign congenital anomalies resulting from the maldevelopment of the primitive foregut. They are usually found above the diaphragm, predominantly in the mediastinum. They are extremely rare in the subdiaphragmatic region, especially in the retroperitoneal location. In a thorough search of MEDLINE, only 27 cases were reported in the English literature.[1-5] It occurs in both sexes in equal ratio and a wide age range. Retroperitoneal bronchogenic cyst can be successfully excised by either open or laparoscopic surgery. Laparoscopic excision is a less aggressive approach and can shorten the hospital stay.[4]

CASE

A 55-year-old man was incidentally found to have a left adrenal solid tumor during physical check up. Half a year later, abdominal CT showed a slight enlargement of the solid tumor (Figure 1). Therefore, he was admitted to our hospital for surgical intervention. On physical examination, the patient was a well-developed Taiwanese man with a pulse rate of 78 beats/minute and a blood pressure of 130/90 mm Hg. Complete blood counts, liver enzymes, renal enzymes, and serum electrolyte levels were within normal limits. No clinical symptoms or signs were noted in this patient, and the preoperative level of vanilmandelic acid (VMA) in the urine was 1.98 mg/day (normal range: 1.00-7.50 mg/day). His past medical history was not significant.

Laparoscopic adrenalectomy was performed. During operation, a 4.0-cm cystic mass was discovered adherent to a normal looking adrenal gland. The cyst with adherent adrenal gland was excised from the kidney. The cyst contained thick proteinaceous fluid. The postoperative course was uneventful and the patient was discharged five days later.

Gross examination of the specimen revealed a collapsed, previously bisected, slight grey-to-brown cyst measuring 4.0 x 3.0 cm, with a maximum wall thickness of 0.2 cm. A compressed adrenal gland with an adjacent small amount of soft tissue measuring 4.0 x 2.0 cm was attached to the cyst (Figure 2).The entire cyst and adrenal gland were submitted for microscopic examination.

Histologically, the cyst wall was lined by pseudostratified ciliated columnar epithelium resting on fibrous connective tissue with focal nodules of mature cartilage. No cytological atypia was noted in the lining epithelium or underlying stromal tissue. These findings were consistent with a bronchogenic cyst (Figure 3). The adjacent adrenal gland showed no specific pathological change.

DISCUSSION

Bronchogenic cysts are rare cystic congenital malformations with ciliate pseudostratified columnar epithelium similar to those of the bronchial wall. Most

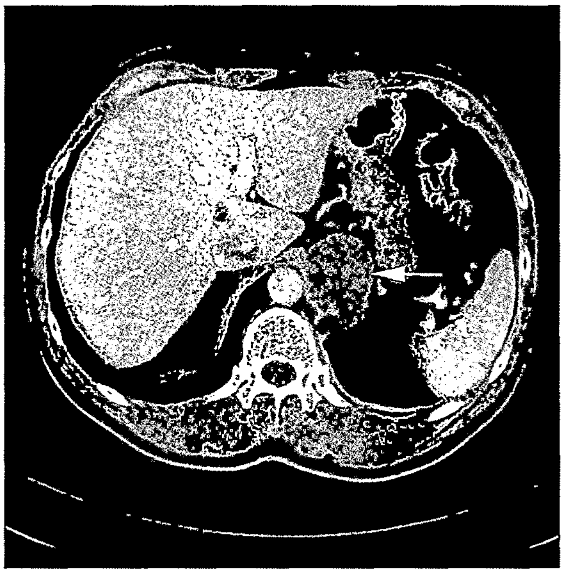

Figure 1. Half a year later, following abdominal contrast enhanced computerized topography reveals slight enlargement of the solid tumor (arrow).

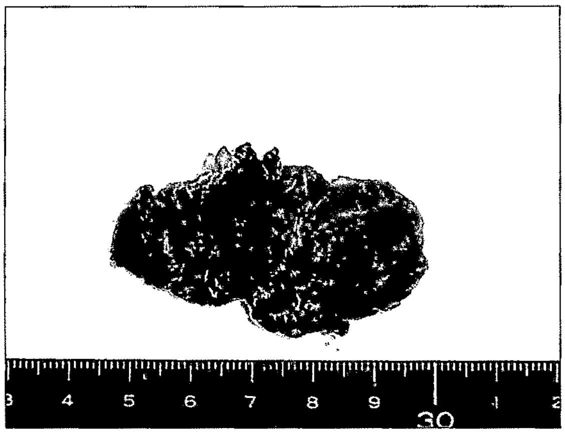

Figure 2. Gross photograph of the retroperitoneal bronchogenic cyst showing para-adrenal location and unilocular cystic lesion.

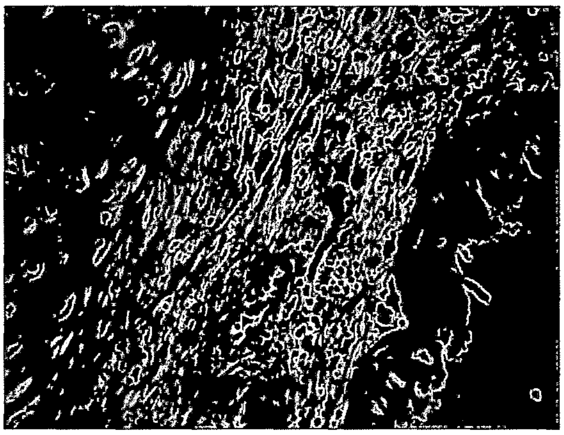

Figure 3. Miscroscopic section of the resection specimen showing a bronchogenic cyst lined with ciliate pseudostratified columnar epithelium. The wall is made up of fibrous connective tissue with a piece of mature cartilage nearby (H&E, original magnification x 400).

bronchogenic cysts originate in the mediastinum; a subdiaphragmatic location is exceptionally rare. Only 27 cases of retroperitoneal bronchial cysts have been reported in the English literature prior to this report. Retroperitoneal bronchogenic cysts occurred in both sexes in equal ratio and a wide age range.

The exact pathogenesis of a retroperitoneal location of a bronchogenic cysts is still unclear. In 1985, Sumiyoshi et al[6] proposed that the tracheobronchial tree may tear off during embryonic migration after fusion of the thoracic and abdominal cavity by the pleuroperitoneal membrane. The tracheobronchial tree, which is pinched off in the retroperitoneal cavity results in a retroperitoneal bronchial cyst.

Preoperative diagnosis of retroperitoneal bronchogenic cyst is very difficult; most of them are diagnosed incidentally. Our case was initially diagnosed as an adrenal solid tumor according to CT images and turned out to be a bronchogenic cyst. The possible explanation for the discordant findings in the image study was the thick proteinaceous fluid content in the cyst. Based on the clinical and radiological information, a differential diagnosis from adrenal cortical or medullary tumors, enteric cysts, pancreatic cyst, bronchopulmonary sequestration, and cystic teratoma, is often elusive. Histopathological examination usually results in an accurate diagnosis. An absence of three different germinal layers in our case precludes the diagnosis of cystic teratoma. Bronchopulmonary sequestration is usually composed of a bronchial component with lung parenchyma and pleural investment, which is absent in our case.

The treatment of choice for retroperitoneal bronchial cysts is surgical excision, which can relieve symptoms, establish a diagnosis and prevent complications, such as infection or malignant transformation.[5] Laparoscopic surgery has become a more common daily practice for surgeons, and therefore, may serve as a less destructive diagnostic and treatment method for retroperitoneal cystic masses.

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case report

Brugada syndrome: an unusual cause of syncope in a young patient

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Syncope is a sudden and transient loss of consciousness associated with loss of postural tone from which recovery is spontaneous.[1] The most common cause of syncope in the general population is neurocardiogenic followed by primary arrhythmias.[2] In the presence of underlying heart disease, syncope is associated with a high rate of mortality.

Sudden cardiac death (SCD) is a witnessed cardiac arrest within 1 hour after the onset of acute symptoms or unexpected, un-witnessed death in a patient known to have been well within the previous 24 hours.[3] It occurs with an approximate incidence of 1 per 1000 inhabitants per year in the West.[4] The leading cause of SCD is ventricular fibrillation secondary to either acute ischemic events or underlying structural heart disease. However, no identifiable cause could be found in 10% of these victims during autopsy or during extensive evaluation of surviving cases.[4]

Brugada syndrome is a new clinical entity first described by Brugada and Brugada in 1992.[5] This syndrome is responsible for approximately 4% of all SCD and 20% of SCD in patients without structural heart disease.[6] It is now considered an important cause of syncope among young patients.

CASE

A 19-year-old male laborer, previously healthy, presented to our emergency department due to sudden loss of consciousness and falling down after emotional stress. This lasted for few seconds as described by his companion who witnessed the event. There was a history of brief palpitation, but he denies any chest pain, shortness of breath or seizures. The patient retained consciousness rapidly, without headache or confusion, but could not recall the event exactly. He reported no similar attacks before, and had no family history of syncope, epilepsy, or sudden unexplained death.

On examination the patient was a young, well-built and healthy male. His blood pressure was 137/82 mm Hg, heart rate was 124 beats per minute and he had a regular respiratory rate 16 breaths per minute and temperature of 36.8°C. The heart, chest, abdomen and lower limb examination were normal. Neurological evaluation showed no focal deficit. The electrocardiogram showed sinus tachycardia, right bundle branch block pattern, and coving type ST-segment elevation in the precordial leads V1, V2 and V3, which is characteristic of Brugada syndrome type 1 (Figure 1A).

The patient was hospitalized and investigations showed a normal creatinine kinase, troponin I, prolactin, a negative toxicology screen, and other routine laboratory tests were normal. X-rays, electroencephalogram and echocardiography were also within normal ranges. He was monitored at the Coronary Care Unit for four days. The ST segment elevation on the ECG returned to normal on the second day. No arrhythmias were reported during this period, but he was stratified in the high-risk group for future arrhythmias.

A cardioverter defibrillator was implanted and he was discharged from the hospital 2 days later. He was followed up at our outpatient clinic after 6 days, at which time the ECG was normal (Figure 1B) and the patient was free of symptoms. He was seen again 3 months later due to viral pharyngitis and was asymptomatic but his ECG showed fever-induced ST-segment elevation in V1 (Figure 1C).

DISCUSSION

Brugada syndrome is a type of cardiac membrane channelopathy. The overall prevalence among the normal population is not established because the ECG is dynamic and there are concealed forms of this syndrome.[7] Some studies report its prevalence to be about 0.05% to 0.6%.[8,9] However, this prevalence is higher in south Asia than in Europe and the United States.[10]

Brugada syndrome is a familial disease. About 60% of patients with Brugada syndrome have a family history of sudden death or have family members with the

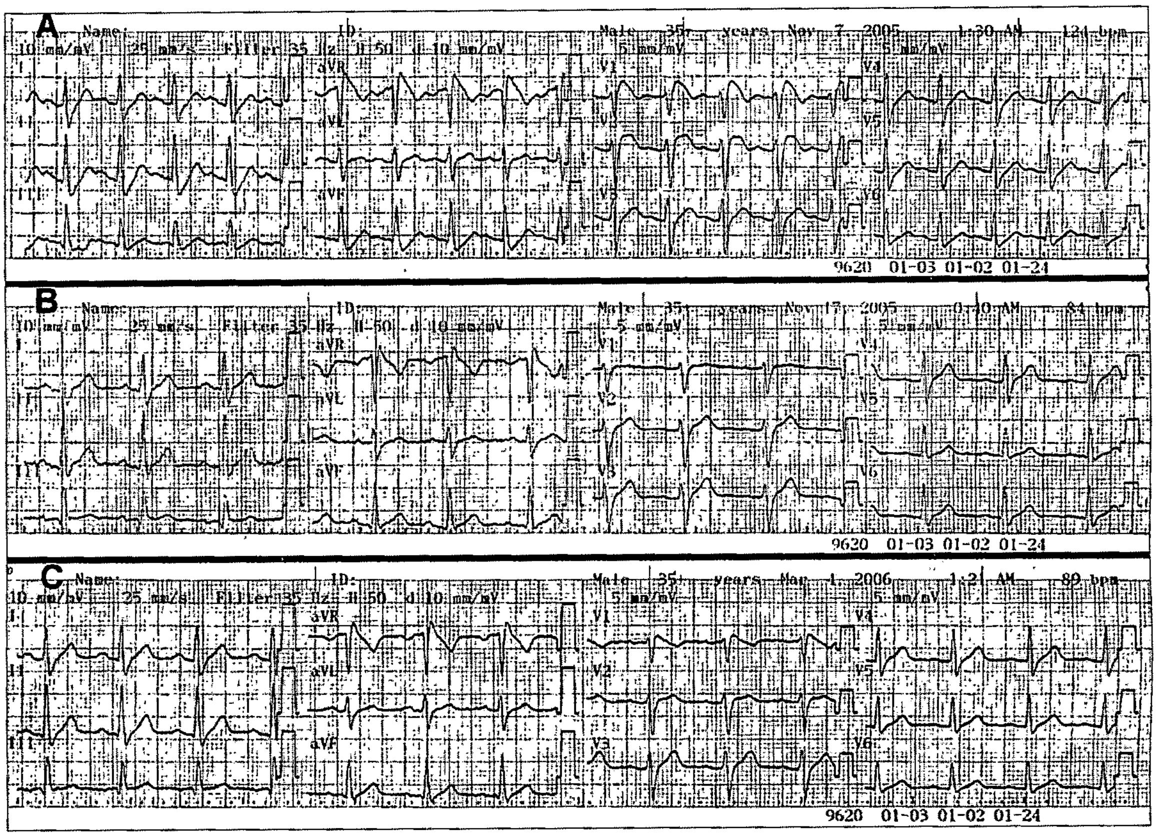

Figure 1. (A) The characteristic ECG of Brugada syndrome. (B) During follow-up. (C) During febrile illness.

ECG pattern of Brugada syndrome. Forty percent of patients have sporadic de novo mutations.[11] It is inherited as autosomal dominant disease with variable penetrance. Chen and coworkers described the genetic nature of the disease and its association to a mutation in the cardiac sodium channels.[12] About 80 mutations have been linked to the gene SCN5A.[13-16]

The exact electrophysiologic mechanisms of this syndrome are not fully understood. Prominent transient outward potassium current (Ito) in the right ventricular epicardium results in marked shortening of the duration of the action potential causing a voltage gradient within the endocardium which results in the ST elevation on the ECG. The voltage gradient may result in reexcitation (phase 2 re-entry) of the epicardium, which triggers ventricular arrhythmias. The sodium current (INa) opposes the potassium current (Ito) during phase 1 of the action potential. The faster inactivation of the sodium channel or the lack of function caused by the mutation explains why an unopposed current (Ito) becomes prominent and markedly shortens the duration of the action potential at the epicardial level.[17]

Patients with Brugada syndrome may be asymptomatic and diagnosed accidentally, or present with syncope. Unfortunately, in some patients, SCD might be the first presentation of the disease. It usually manifests during adulthood with a male predominance (male to female ratio, 8:1). The mean age of sudden death in victims of Brugada syndrome is about 35 to 40 years.[11] All clinical manifestations of Brugada Syndrome are attributed to ventricular tachyarrhythmias and their complications. Mostly, these arrhythmias occur at rest or during nighttime.[11]

Brugada syndrome is diagnosed, after exclusion of structural heart disease, when there is a documented history of one of the electrocardiographic or clinical events (Table 1) in association with a type 1 ECG pattern.[6] These ECG changes are variable over time, depending on the autonomic interaction and the administration of antiarrhythmic drugs.[18] Our patient fulfilled the diagnostic criteria for Brugada syndrome and needed no further invasive diagnostic tests. As he developed syncope, he most likely developed VT/VF that terminated spontaneously, which is a common presentation in Brugada syndrome.

There are three ECG patterns used to diagnose Brugada syndrome. All have a J-wave amplitude ≥2 mm. Type 1 is characterized by the coving type ST-segment elevation in the precordial leads V1, V2 and V3, followed by T wave inversion. Type 2 shows a saddleback ST-segment elevation in leads V1, V2 and V3, but the downward displacement of the ST-segment lies between the two elevations of the segment but does not reach the baseline and the T-wave could be positive or biphasic. Type 3 shows the same saddleback ST-segment as in type 2, but touches the baseline and the T-wave is always positive.[19]

The presence of a type 1 ECG pattern in asymptomatic patients is sufficient to diagnose this syndrome in the absence of other temporary conditions that may provoke ECG patterns that mimic Brugada syndrome (Table 2). The pharmacologic provocation test is not indicated in these patients as it has neither diagnostic nor prognostic values yet.[19,6] However, genetic testing is recommended to support the clinical diagnosis, and for early detection of relatives at potential risk.[6] On the other hand, in patients with type 2 and 3 ECG patterns, the drug challenge test is recommended to clarify the diagnosis. It is considered positive if type 2 or 3 converted to type 1, while conversion of type 3 to type 2 after the drug challenge is considered inconclusive.[19]

The normal resting ECG is not sufficient to exclude the presence of Brugada syndrome, especially in family members of a patient with this syndrome or patients with unexplained syncope. Therefore, the drug provocation test is recommended. It can be done by administering a sodium channel blocker like ajmaline, flecainide, procainamide or pilsicainide under intensive monitoring conditions. The test is considered positive if there is an additional 1-mm ST-segment elevation in the right precordial leads V1, V2 and V3.[20] Placement of the right precordial leads in a superior position in the second intercostal space can increase the sensitivity of the ECG for detecting the Brugada phenotype in some patients with or without administering sodium channel blockers.[21]

Contrary to the fact that vagal stimulation and bradycardia increase ST-segment elevation in Brugada syndrome, and that adrenergic stimulation or tachycardia decrease or may even normalize the ST-segment elevation,[22] our patient developed syncope after a stressful condition, which is characterized by sympathetic overstimulation. His ECG showed the characteristic ECG of Brugada syndrome while his heart rate was 125 beats per minute. On the other hand, there is growing evidence that Brugada syndrome is unmasked by fever,[23] which was noted in our patient.

Brugada syndrome is now considered different from arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) in both its clinical presentation and genetic predisposition.[19] Drug challenge may be useful in discriminating between the two diseases.[24] While Brugada syndrome and sudden unexpected death syndrome (SUDS) are the same entity, they share a lot of genetic, clinical, electrocardiographic and prognostic properties.[10]

Table 1. Electrocardiographic and clinical events complicating Brugada syndrome.

- Documented ventricular fibrillation
- Polymorphic ventricular tachycardia
- Family history of sudden cardiac death
- Coved-type ECGs in family members
- Inducibility of ventricular tachycardia with programmed electrical stimulation
- Syncope
- Nocturnal agonal respiration

ECG: electrocardiogram

Table 2. ECG abnormalities mimicking Brugada syndrome.

- Atypical right bundle-branch block
- Left ventricular hypertrophy
- Early repolarization
- Acute pericarditis
- Acute myocardial ischemia or infarction
- Pulmonary embolism
- Prinzmetal angina
- Dissecting aortic aneurysm
- Central and autonomic nervous system abnormalities
- Duchenne muscular dystrophy
- Thiamin deficiency
- Hyperkalemia
- Hypercalcemia
- Arrhythmogenic right ventricular dysplasia/cardiomyopathy
- Pectus excavatum
- Hypothermia
- Mechanical compression of the right ventricular outflow
- Well-trained athletes
- Cocaine intoxication

The list of drugs that can cause Brugada-like ST-segment elevation is expanding. These drugs include some antiarrhythmic, antianginal, psychotropic and addiction drugs, but it is not known if there is a genetic predisposition for these patients.[6]

Programmed electrical stimulation (PES) reproducibility induces VT or VF in almost all Brugada syndrome patients with a history of aborted sudden death or syncope.[25] But, shall we extend the electrophysiological testing to the family members and asymptomatic patients? Despite the belief that the inducibility of VT/VF in electrophysiological studies may stratify asymptomatic patients with Brugada syndrome into the high-risk group,[26] and mandates the need for implantation of implantable cardioverter defibrillator (ICD), other

Table 3. Treatment options for patients with Brugada syndrome.

Clinical	Family History	ECG	EPS	Treatment
Symptomatic	-	-	-	ICD
Asymptomatic	-	-	Inducible VT/VF	ICD
Asymptomatic	Positive	Spontaneous	Negative	? ICD
Asymptomatic	Negative	Spontaneous	Negative	Observation
Asymptomatic	Negative	Drug-induced	Negative	Observation

ECG: electrocardiogram, EPS: electrophysiologic study, VT/VF: ventricular tachycardia/fibrillation.

studies failed to support this hypothesis.[27-29] Brugada and coworkers found that inducibility of sustained ventricular arrhythmias during PES is a powerful predictor of outcome in Brugada syndrome.[30,31] They concluded that symptomatic patients require protective ICD implantation because of the high incidence of arrhythmic events, independent of the results of the PES, for which the test could simply be avoided. Asymptomatic patients can be reassured if they are non-inducible,[31] while asymptomatic patients with positive PES should undergo ICD implantation.[32] So, EPS is recommended in all asymptomatic patients with Brugada syndrome.

Implantation of cardiac defibrillator is the only effective intervention for preventing sudden cardiac death in Brugada syndrome.[25] It is recommended for all symptomatic patients. Although repeated episodes of polymorphic ventricular tachycardia can be treated with isoproterenol or quinidine,[11,33] other antiarrhythmic drugs do not protect against sudden cardiac death in Brugada syndrome.[11] Indications for ICD are summarized in Table 3.

Brugada syndrome is associated with a high prevalence of malignant arrhythmias and sudden death. The presence of Brugada ECG by itself is a risk for arrhythmic events, and normalization of the ECG during follow up does not indicate a better prognosis.[17] Patients with spontaneous Brugada ECG and a history of aborted sudden cardiac death or syncope are at highest risk for development of these arrhythmias.[16] Asymptomatic individuals with spontaneous Brugada ECG are also at high risk for arrhythmic events if sustained ventricular arrhythmias are induced during EPS, while asymptomatic patients have a benign prognosis if the EPS is negative.[32]

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case report

Recurrent posterior reversible encephalopathy syndrome in a patient with sickle cell disease

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Posterior reversible encephalopathy syndrome (PRES) refers to a clinicoradiologic entity with characteristic features on neuroimaging and nonspecific symptoms comprising headache, confusion, visual disturbances and seizures.[1,2] This syndrome may occur in diverse situations, including hypertensive encephalopathy, eclampsia, and the use of cytotoxic and immunosuppressive drugs. The lesions in PRES are thought to be due to vasogenic edema, predominate in the posterior cerebral hemispheres, and are reversible with appropriate management. We present the case of a young male with sickle cell disease (SCD) who had recurrent episodes of this syndrome in association with repeated priapism, sickle cell nephropathy and hypertension. Though the association of SCD, priapism, exchange transfusion and neurological events has been described previously,[3] the occurrence of recurrent PRES in SCD preceded by episodes of priapism has not been reported before.

CASE

A 20-year-old male with SCD presented to our accident and emergency department with sudden onset of severe headache, blurred vision and confusion. There was no fever, vomiting, jaundice, rash or chest symptoms. He had had multiple episodes of priapism in the recent past and had been treated with exchange transfusion and intracorporal adrenaline. On examination, the patient was afebrile but drowsy. His pulse was 90/minute and blood pressure 220/110 mm Hg. He perceived moving objects at 2 to 3 feet and his pupils were normally reactive. He did not have papilledema or obvious cranial nerve palsies and was moving all his limbs. His deep tendon reflexes were normal, plantars were flexor and he had no meningeal signs. Laboratory investigations were normal except for (normal values in parenthesis) low serum albumin 20 g/L (35-50 g/L), serum creatinine 148 μmol/L (62-140 μmol/L) and blood urea 7.5 mmol/L (3-7 mmol/L). His hemoglobin was 11.1 g/dL (13-15.5 g/dL), platelet count 339 (140-440×10^9) and serum lactic dehydrogenase [LDH] was 152 u/L (135-225 u/L). The hemoglobin pattern by electrophoresis showed HbA 69.1%, HbA2 3.5%, HbS 17.7% and HbF 2.0%.

A plain CT scan of the brain showed small poorly defined hypodense areas in both occipital lobes involving the grey and white matter. On account of his sickle disease status and hypertension, a differential diagnosis of infarcts or PRES was entertained and MRI of the brain including MR venography [MRV] was done about six hours after the CT scan. The T2 and fluid attenuated inversion recovery [FLAIR] sequences showed multiple hyperintense lesions in the parietal and occipital lobes involving both grey and white matter (Figures 1.1 and 1.2). The rest of brain including the MRV was normal. Diffusion weighted imaging [DWI] was not available. A diagnosis of possible PRES was made. The patient was managed with lowering of blood pressure with captopril and nitroglycerin infusion. Investigation of his hypertension revealed that the patient had gross proteinuria. Urinary creatinine was 4042 μmol/L with serum creatinine 170 μmol/L (62-140 μmol/L), urine osmolality 358 mosm/kg (850-1000 mosm/kg), creatinine clearance 0.63 mL/sec (1.62-2.8 mL/sec) and 24-hour urine protein of 9.9 g/day (0.05-0.1 g/day). Ultrasound of the abdomen showed normal-sized kidneys with mildly echogenic cortex, suggesting renal parenchymal disease. The rest of abdomen was normal with no other cause for hypertension. The patient underwent renal biopsy and histopathology showed a membranoproliferative pattern of sickle cell nephropathy with marked tubulo-interstitial changes and normal blood vessels.

MRI of the brain repeated about two weeks after admission showed significant resolution of the previously identified lesions (Figures 1.3 and 1.4); at this time, the patient was much better and his hypertension was fully controlled on oral antihypertensives. He was not given

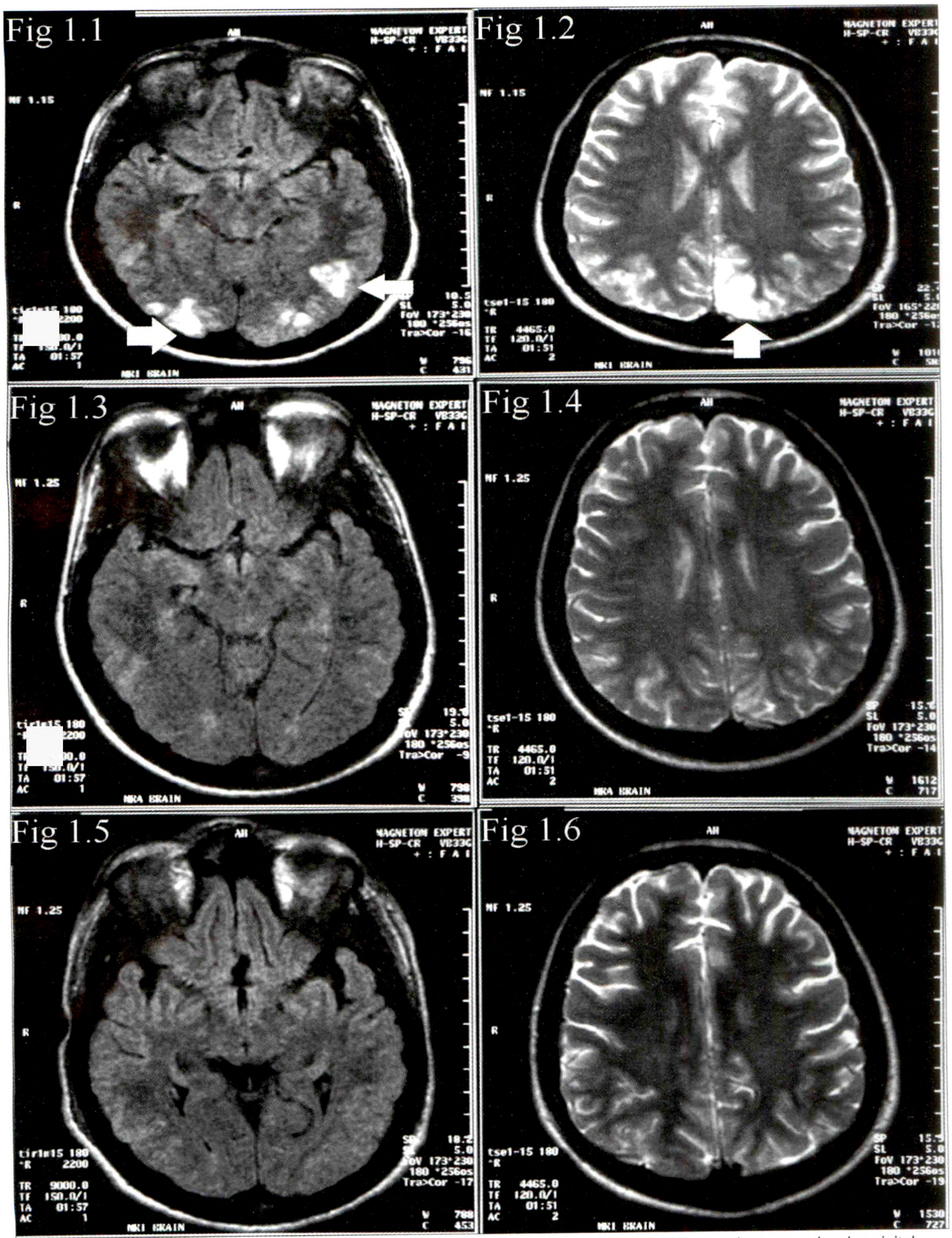

Figure 1. FLAIR (1.1) and T2 (1.2) images of initial MRI study showing hyperintense lesions in the posterior temporal and occipital lobes. Follow-up MRI 2 weeks later (1.3 and 1.4) shows partial resolution of the lesions. Total resolution of the abnormalities is seen on MRI 6 weeks after the onset (1.5 and 1.6).

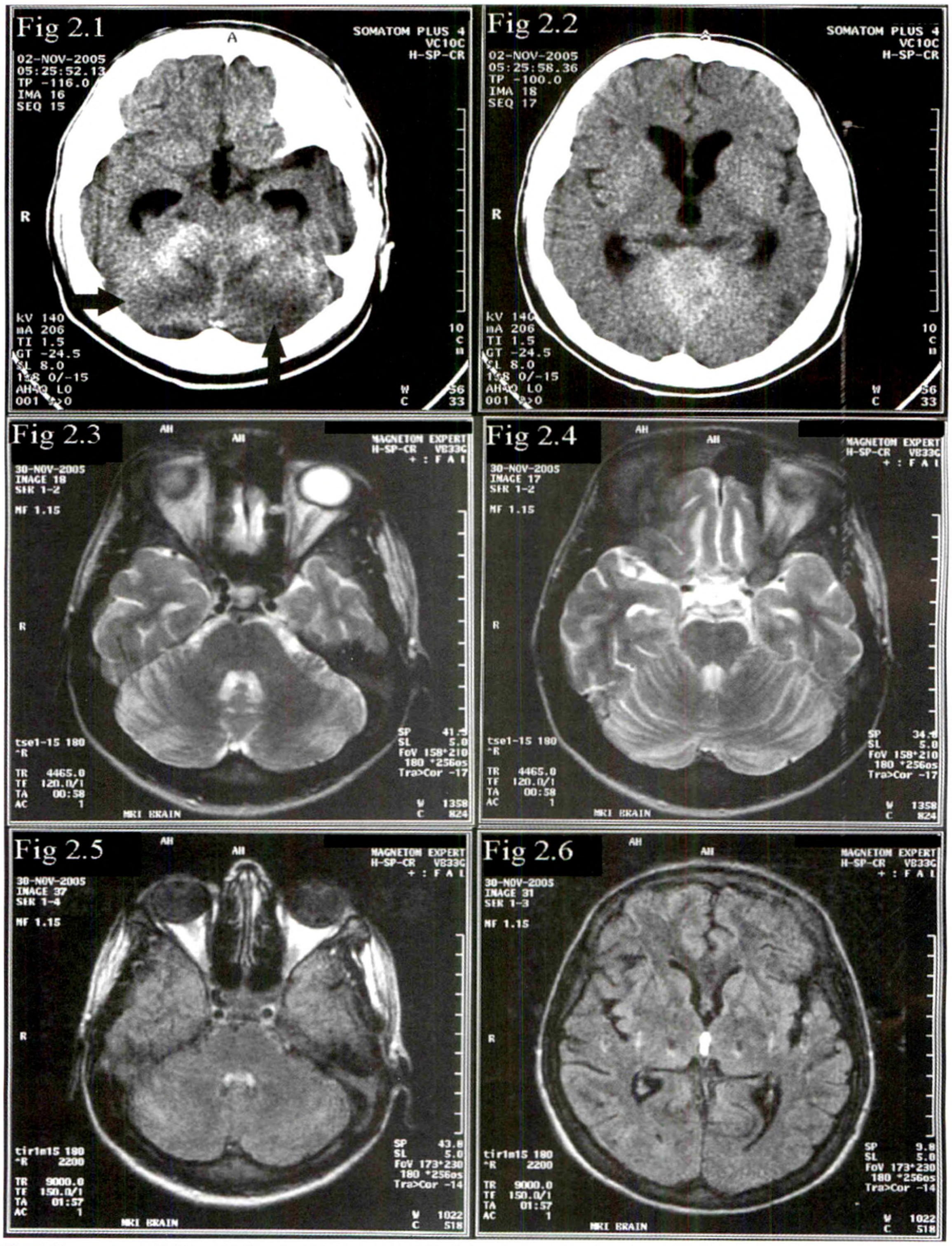

Fig 2. Non-contrast CT (2.1 and 2.2) during third episode of PRES showing hypodensities in cerebellum and mild hydrocephalus due to mass effect on fourth ventricle. FLAIR and T2-weighted images of MRI 4 weeks later show resolution of the lesions and the hydrocephalus (Figure 2.3-2.6).

exchange transfusion as his HbS was only 17.7% and he had received an exchange transfusion in the week preceding his admission for priapism. His nephropathy was managed conservatively. While in the hospital, the patient continued to have episodes of severe headache with periods of sudden loss of vision that recovered completely in a few hours. He also developed isolated episodes of generalized seizures, which were managed with phenytoin and phenobarbitone. At discharge, the patient was free of headaches and his vision was normal and he was advised to continue captopril, phenytoin and phenobarbitone.

Six weeks after his first admission, the patient presented with status epilepticus and had to be intubated and treated with general anesthesia. BP at this presentation was 160/113 mm Hg. A CT of the brain showed new small areas of subtle hypodensity in cerebellum and left parietal region (images not shown). MRI of the brain was obtained a few days later, after treatment with multiple antihypertensives including intravenous labetolol infusion. This MRI showed total resolution of the lesions in the parietal and occipital lobes that were seen in the first MR study (Figures 1.5 and 1.6). The new lesions noted in the CT study were only seen as subtle, small hyperintensities in the left frontal and right cerebellar hemisphere (image not shown). The disappearance of the lesions in the parietal and occipital lobes was fully in keeping with a diagnosis of PRES. The patient had priapism twice while in the hospital and both episodes subsided spontaneously. About two weeks into his admission to the hospital, the patient had a sharp elevation of BP (224/112mm of Hg) and became very drowsy. A brain CT showed extensive cerebellar hypodensity with a mass effect, resulting in effacement of the fourth ventricle (Figures 2.1 and 2.2). He improved with lowering of BP. MRI of the brain obtained four weeks after the CT scan was normal (Figures 2.3 and 2.4). The disappearance of the cerebellar lesions with control of BP was once again consistent with PRES. This patient thus had recurrent PRES, with the first episode typically sited in the parietal and occipital lobes, the second episode presenting as status epilepticus with less pronounced changes in the cerebellum on imaging and the third episode producing marked edema in the cerebellum, causing hydrocephalus. All episodes responded to lowering of BP. At last review, BP was controlled, but the patient had mild cerebellar ataxia and could walk with support.

DISCUSSION

The terms posterior reversible leukoencephalopathy, reversible posterior cerebral edema syndrome, and posterior reversible encephalopathy syndrome refer to a clinicoradiologic entity characterized by headaches, altered mentation, visual disturbances, seizures, and transient changes in posterior cerebral hemispheres on neuroimaging.[1,2] This syndrome was first reported by Hinchey et al in 1996,[1] who referred to the condition as reversible posterior leukoencephalopathy [RPLE] syndrome. Casey et al[2] thought the term leukoencephalopathy was misleading, as there is usually no accompanying destructive process of the white matter. He proposed that the condition be referred to as PRES. Though the changes in a typical case of PRES are reversible, it can progress to ischemia, cerebral infarction and even death.[4]

PRES can occur in various situations. In patients with hypertensive encephalopathy and in pregnant patients with eclampsia, PRES is thought to occur after a subacute elevation in blood pressure.[1,5] In the setting of uremia, hemolytic-uremic syndrome, and thrombotic thrombocytopenia purpura, endothelial toxins are thought to play a role in the development of PRES.[1,4,6] Cyclosporine and tacrolimus are the drugs most frequently associated with the development of PRES, others being cisplatin, gemcitabine, and combination chemotherapy regimens.[7] PRES has also been described with *Mycobacterium avium intracellulare*-related hypercalcemia in AIDS.[8]

The underlying pathophysiologic mechanism in uncomplicated PRES is thought to be vasogenic edema due to cerebrovascular autoregulatory dysfunction.[1,2,9] The predilection for involvement of the posterior circulation territories results from the relatively sparse sympathetic innervation of the vertebrobasilar circulation.[4,10] In a healthy subject, brain perfusion is maintained by both myogenic and neurogenic mechanisms.[5] In patients with PRES, the myogenic response is blunted by passive overdistention of the vessel due to elevations in BP or direct toxic effects on the endothelium.[4,9] The cerebral autoregulatory mechanisms then become more dependent on the neurogenic response. The more poorly innervated areas in the posterior circulation are therefore more vulnerable to the leakage of fluid into the interstitium and vasogenic edema.[4,5]

In contrast to the nonspecific clinical findings of PRES, the MRI pattern is often characteristic and represents an essential component of the diagnosis.[11] Typically, the lesions of PRES predominate in the parieto-occipital white matter, with some involvement of the overlying cortex and are hyperintense on T2-weighted and FLAIR images. In diffusion-weighted images, they are usually hypointense or isointense with an increase of the apparent diffusion coefficient [ADC], indicating vasogenic edema.[2,10] Follow-up MRI after appropriate therapy for the cause of PRES shows resolution of the lesions, unless the condition progresses to infarction or hemorrhage. PRES lesions involving the occipital lobe spare the calcarine and paramedian occipital lobe. This feature, along with the predominant involvement of white matter helps to distinguish this syndrome from bilateral infarctions of the posterior cerebral artery.[1] Though the lesions in PRES predominate in the territories supplied by the posterior circulation, other areas of the brain like the frontal and temporal lobes, cerebellum, thalamus and brainstem may also be involved.[1,2,4,12] When regions of the brain other than the parieto-occipital lobes are predominantly involved, the syndrome can be called atypical. In such cases, a diffusion-weighted MRI with ADC mapping shows increased ADC values representing vasogenic edema in these areas, thus differentiating atypical PRES from other brain disorders that affect the same sites, causing cytotoxic edema with reduced ADC values.[13] As we could not obtain a diffusion-weighted image, the diagnosis of PRES could only be confirmed in our patient by resolution of the changes on follow-up imaging.

Though SCD is common, the incidence of PRES is apparently low. A case series of children with SCD presenting with acute chest syndrome had three children with PRES, all of whom had high blood pressure recordings.[14] To the best of our knowledge, the occurrence of recurrent PRES in SCD in conjunction with recurrent priapism and sickle glomerulopathy has not been described before. It lends credence to the observation of the clustering of neurological events in patients with SCD with priapism treated with exchange transfusion. ASPEN syndrome, an eponym for association of SCD, priapism, exchange transfusion and neurological events has been described previously. The neurological events are thought to be related to cerebral ischemia after an acute increase in total hemoglobin percentage, with a concomitant decrease in percent hemoglobin S and subsequent release of vasoactive substances during penile detumescence.[3] About 5% to 18% of patients with SCD develop renal failure.[15] Sickle cell glomerulopathy shows a picture of glomerular hypertrophy and focal glomerulosclerosis.[16] Basement membrane lucencies and areas of apparent duplication are seen, which present a membranoproliferative glomerulonephritis (MPGN) like picture.[17] There is an increased risk of multiorgan failure, including kidney failure in patients with SCD who have episodes of priapism, especially in those with postpubertal presentation.[18] Our patient had repeated admissions for priapism prior to developing PRES. We also found that he had high blood pressure recordings during each of his presentations with priapism. Kato et al have noted that steady-state LDH elevation identifies a subset of patients with SCD at risk for pulmonary hypertension, cutaneous leg ulceration, priapism and early death.[19] Our patient had normal LDH throughout his episodes of PRES and also during his admissions for priapism.

In summary, we have presented the case of a young male with SCD who developed recurrent PRES following frequent episodes of priapism and acute hypertension secondary to sickle nephropathy. This case highlights the need to expect neurological events in patients with SCD who present with recurrent priapism. It is imperative that the syndrome of PRES is correctly recognized on neuroimaging, as the condition is reversible and potential complications like cerebral infarction and death can be avoided with appropriate therapy.

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case report

Umbilical hernia associated with extracelomic intestinal atresia and perforation of the ileum in a newborn

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The umbilicus is the site of various embryological defects involving the midgut (herniation), abdominal wall, vessels and urachus. Hernia of the umbilical cord has been recognized as a distinct entity occurring at a specific embryological step.[1] Occasionally it is associated with patent vitello-intestinal duct (PVID) anomaly.[2] We report the first case of umbilical hernia in a neonate associated with ileal atresia complicated by intestinal perforation, meconium staining of liquor and meconium aspiration syndrome.

CASE

A male baby weighing 1750 g at 33 weeks gestation was born to a 28-year-old mother (G3P2) with meconium-stained liquor. The baby had meconium aspiration syndrome for which he received ventilatory support in the level 3 nursery at Maternity and Children's Hospital. The baby was found to have a discharge of meconium from an opening in the gut protruding from the umbilical ring into the cord. There were black-colored tubular structures present within the cord close to the umbilical clamp (Figure 1). The baby was active and vitals were maintained. No other gross congenital anomalies were detected. Considering possible iatrogenic gut injury due to umbilical clamp, an urgent exploration was carried out under general anesthesia. Intraoperatively, a type 3A atresia of the distal ileum (Figure 2) was found in the extracelomic gut (in the umbilical cord). Approximately 20 centimeters of proximal ileum was grossly dilated with perforation at the end. The distal segment was hypoplastic with a gap in the mesentery. Saline irrigation into the distal segment revealed normal patency of the rest of the gut and strings of white mucus. The black, shriveled tubular structures between the two ends of the atresia were excised and sent for histopathological examination. The dilated segment of the ileum was excised and an ileo-ileal anastomosis was done. The post-operative course was uneventful. At 5 months follow up the baby was doing well. Histopathology reported the black tubular tissues as atrophic intestine.

DISCUSSION

A varied number of anomalies affect the umbilicus. Umbilical cord hernia is a distinct but poorly defined anomaly where the midgut is found herniating into the substance of the umbilical cord. Unlike omphalocele and gastroschisis, there is no deficiency of the anterior abdominal wall. Also there is an absence of association with congenital anomalies, namely cardiac, chromosomal anomalies (in omphalocele) and intestinal atresias (gastroschisis) in patients with umbilical cord hernia. It originates at an early stage of embryogenesis and therefore may be detectable by fetal ultrasonography as early as the second trimester.[1] Interestingly, this early embryopathy persists throughout the rest of gestation as a stable umbilical mass.[1] At birth, it is mostly misdiagnosed as a 'small omphalocele' by many or brought to the attention of the pediatric surgeon after accidental injury to the gut by an umbilical clamp. Usually the contents are bowel, the hernia is reducible and anatomically the umbilical ring is complete, but may be somewhat wide. Neonatal correction is easy and cures the problem. Otherwise spontaneous epithelialisation of the coverings of the hernia would form a 'cutis navel'. In addition to this benign presentation of umbilical hernia, there have been reports of associated PVID producing meconium discharge in the perinatal or commonly in the postnatal period.[2]

Animal as well as autopsy studies on human fetuses have established the etiogenesis of ileal and jejunal atresias.[3-6] Frequent clinical instances of intestinal atresias as a result of intrauterine mesenteric vascular insults such as volvulus, intussusception, internal hernia and constriction of the mesentery in a tight gastroschisis or omphalocele defect have been observed. Atresia due to bowel incarceration in omphalocele[7-9] or umbilical clamping of an occult omphalocele[10] have been reported in the literature. Resorption of the isolated loop of the gut following vascular accident (intracelomic) leads to atresia.[9]

In our case, the initial appearance (Figure 1) was akin to umbilical hernia with PVID with meconium discharge from the cord. The black-colored loop-like structures in the cord and closely applied umbilical clamp seemed to indicate vascular injury to the gut and gangrene. This prompted an early exploration. Intraoperative findings suggested a 'type 3A' ileal atresia (Figure 2) with perforation of the dilated proximal segment of the gut. The distal segment was hypoplastic. The absence of meconium in the distal segment and the presence of whitish mucus strings favored an early fetal vascular accident involving the mesentery and small gut.

We hypothesized that this early vascular accident could be the causative factor for persistence of extracelomic herniation of the midgut and umbilical cord herniation. The blackish loops in the cord were found to be atrophic intestinal loops on histopathology. These might represent the partially resorbed portion of devascularised fetal intestines. This association is a rare occurrence.

Umbilical hernia is a distinct anomaly occurring at a different embryological stage as compared to omphalocele and gastroschisis. Vascular accidents may occur in the extracelomic gut causing formation of intestinal atresia. This may in turn cause persistence of hernia in postnatal life. Delivery room personnel should be aware of this anomaly and apply the clamp at a safe distance to avoid catastrophe. Any thickening of the base of the cord or a small opening on the lateral aspect of the cord should warn about this entity. Babies usually lack other congenital anomalies and surgical correction is simple at birth unless associated with PVID or intestinal atresia.

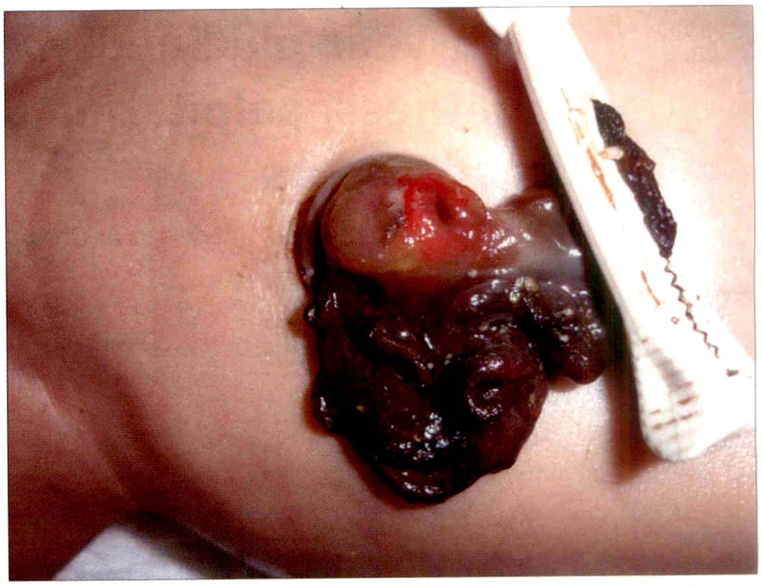

Figure 1. Hernia of the umbilical cord with perforation of the gut and black tubular structures in the cord.

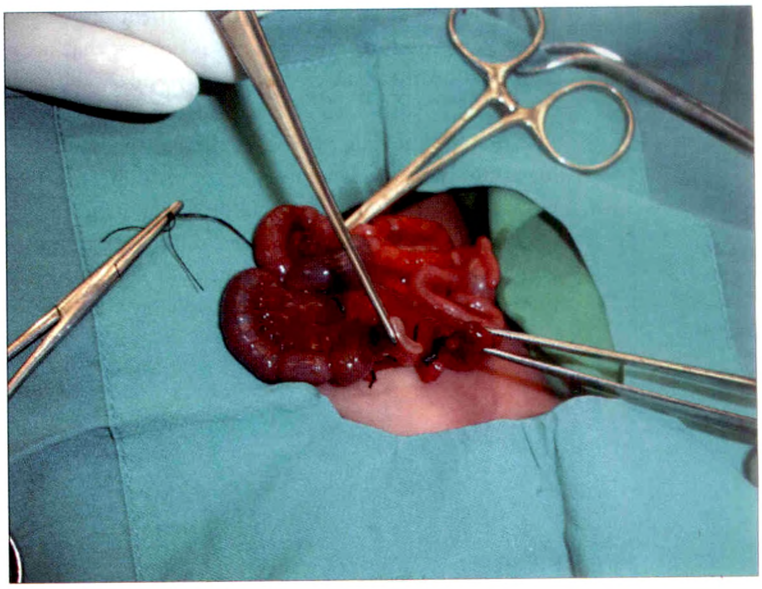

Figure 2. Type 3A ileal atresia.

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what's your diagnosis?

A 29-year-old Saudi male complaining of chest tightness, palpitation and mild dyspnea for the past 3 hours

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A 29-year-old Saudi male, with no known past medical history other than tobacco use, presented to our Emergency Department (ED) complaining of chest tightness, palpitation and mild dyspnea for the past 3 hours. He had a similar episode one year previously, which was associated with near-syncope, and was seen at our ED. The patient discharged himself and no further work up was done at that occasion. His brother had died suddenly while walking at the age of 37 years with no clear cause of death.

The physical examination of the patient was unremarkable. Routine laboratory tests including electrolytes, cardiac enzymes and lipid profile and chest x-ray were within normal limits. ECG showed sinus rhythm with incomplete right bundle branch block (RBBB) and there was ST segment elevation involving V1, V2 and V3 (Figure 1).

A cardiology consult was obtained, and the patient was admitted for observation. Echocardiogram of the heart was normal and the patient was counseled regarding coronary angiography and the implantation of an automatic implantable cardioverter/defrillator (AICD). He was very reluctant regarding AICD placement, but coronary angiography was done and was normal.

The patient was discharged home on no treatment and was advised to come back for AICD placement after having a second opinion, which he suggested, and was also counseled regarding the importance of family testing for the disease.

Answer on page: 223

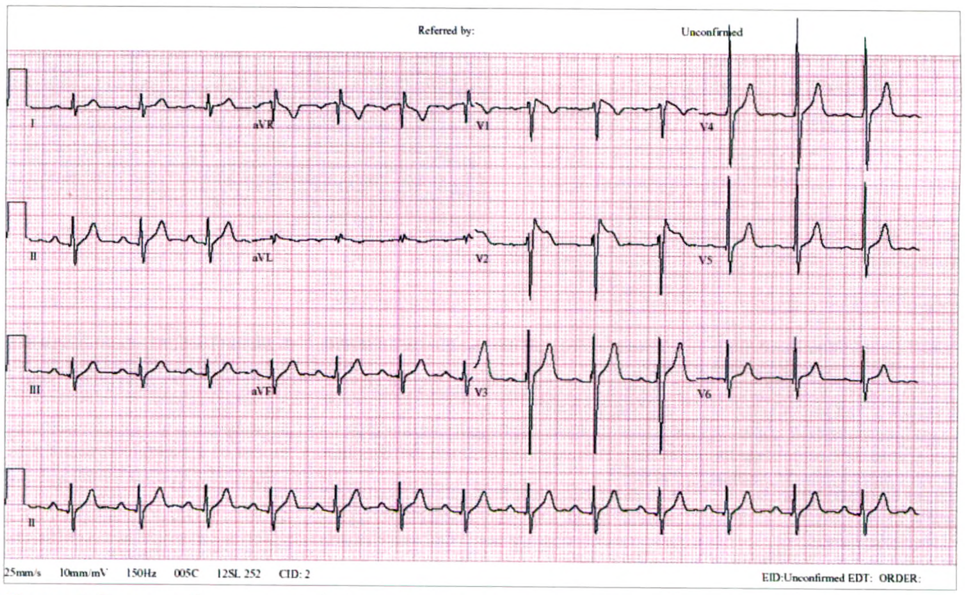

Figure 1. Electrocardiogram on admission to the emergency department.

Rare manifestations of Wegener's granulomatosis

To the Editor: Wegener's granulomatosis (WG) is a necrotizing granulomatous small-vessel vasculitis.[1] The frequency of cardiac involvement in WG varies from 6 to 12 percent.[2] However, the occurrence of ascites and hemorrhagic effusion in WG were not reported in a MEDLINE search.

A 19-year-old man was referred to Baqyatollah hospital with a history of fever and polyarthritis for two weeks. The patient presented with weight loss, productive cough, and hemoptysis. His temperature was 39°C, heart rate 95/min and the respiratory rate was 28/min. A diffuse, coarse crackle was audible over both lungs. Severe joint inflammation was noted. His chest X-ray showed multiple pulmonary infiltration (Figure 1). He was treated for pulmonary abscess with clindamycin and ceftriaxone. The fever subsided gradually, but the polyarthritis, tachycardia, and tachypnea continued. Ultrasound study of the abdomen (Fiugure 2), showed mild splenomegaly and ascites. Moderate pericardial effusion was noticed by echocardiography. In the chest CT-scan, multiple isodense masses were found. Because of his severe clinical condition a high-dose steroid was given. Subsequently, marked hematuria, granular casturia and proteinuria developed.

C-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody) was positive. Pericardial effusion presented with a bloody appearance and the WBC count was 15000/mm^3. Culture and PCR examinations were negative. No organism grew in ascites fluid culture. The WBC count in ascitic fluid was 2500/mm^3, with a PMN value of 75%. A CT-guided lung biopsy was performed. Multiple foci of necrosis and infiltration of macrophages and neutrophils were seen. The diagnosis of WG was made, and combination therapy of high-dose steroid with cyclophosphamide was prescribed. In a few days, his general condition began to show signs of improvement. All clinical, laboratory, and imaging abnormalities also improved. He was discharged after 30 days.

WG is a disease manifested by necrotizing granuloma of the upper respiratory tract, lung, and renal involvement[3] with a 5-year survival rate approaching 95%.[2] Hemopericardium and ascites are a rare clinical picture not previously reported in WG.

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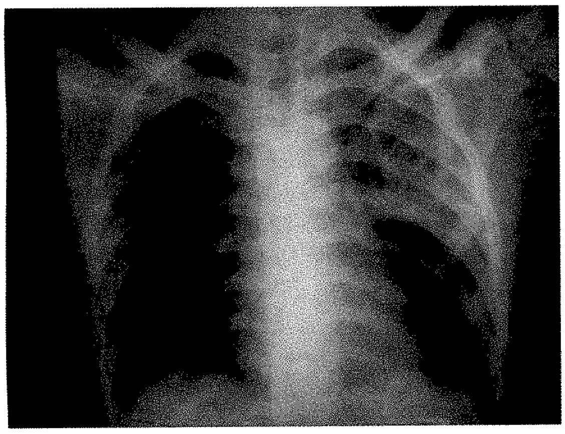

Figure 1. Chest X-ray showing multiple pulmonary infiltrations.

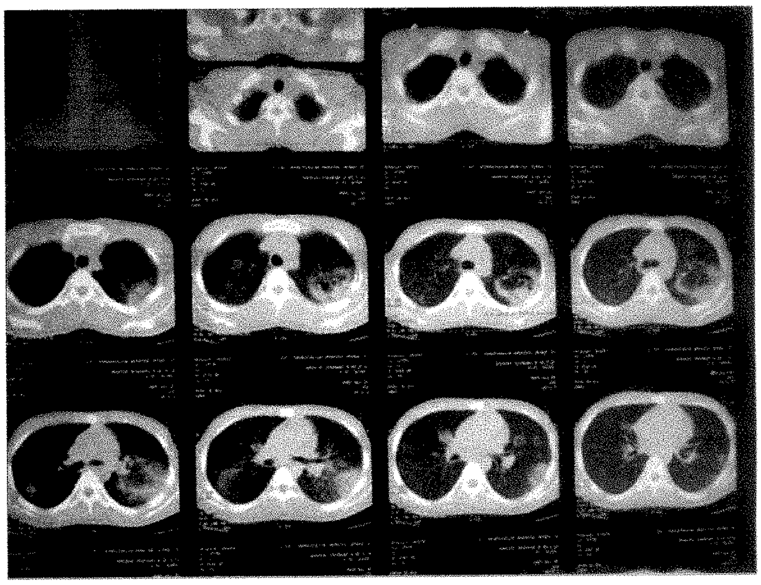

Figure 2. Chest CT scans showing multiple isodense masses.

What explains discrepant gender identity outcome in 46,XX individuals with 11-hydroxylase deficiency?

To The Editor: I read with great interest the report by Bin-Abbas et al[1] of two 46,XX siblings with 11-hydroxylase deficiency (11-OHD) raised male with divergent gender identity (GI) outcome in adolescence. The authors conclude "that the extent of external genitalia virilization, particularly the degree of hypospadias, and not the duration or the level of prenatal and postnatal androgen exposure, is the main gender identity determinant" in 46,XX patients with CAH. I applaud the authors for having based their decisions for and against gender-reassignment in these two siblings on a careful psychiatric evaluation with extensive counseling, but I am concerned that their theoretical conclusions regarding the determinants of GI may lead some clinicians to problematic unifactorial decisions regarding gender assignment and re-assignment.

Clearly, the "extent of external genitalia virilization" determines gender assignment at birth in newborns with normal genital development, and to a considerable extent also in newborns with ambiguous genitalia, especially when sophisticated diagnostic techniques are not readily accessible, as it is common in resource-poor communities. However, the association of the degree of masculinization of the external genitalia with gender identity development is comparably weak, not only in 46,XY, but also in 46,XX individuals, and genital-status-based gender assignment in infancy does not firmly determine GI outcome later. Otherwise we would not see gender dysphoria and patient-desired gender re-assignment in 46,XX 21-OHD-CAH, which occurs–albeit with relatively low incidence–in both female- and male-assigned patients.[2] In my reading of the literature and my clinical experience with 46,XX CAH patients raised female, patient-initiated gender change to male occurs more frequently in patients born with Prader stage 3-4 (clitorophallus with hypospadias) than in patients born with Prader stage 5 (completely masculinized external genitalia). The existence of non-intersex patients with female-to-male transsexualism who typically have entirely normal female genitalia also speaks against a determining role of the external genitalia for GI development.

So, which factors should one consider in explaining the different outcome in the two 11-OHD siblings of Bin-Abbas et al? First of all, the remarkable difference between the siblings in genital development may indicate behaviorally relevant differences in androgen exposure of the developing brain. Given that the two siblings are offspring from the same parents, it is highly likely (albeit not absolutely certain) that the molecular abnormality of the 17-OHD gene is identical in both. Nevertheless, the high local androgen concentration required at the early critical period of genital differentiation for the formation of a penile urethra[3] was apparently not present in the older sibling, although later in development the androgen levels were high enough to promote substantial growth of a clitorophallus. We do not know how late during the fetal development of this patient the androgens increased to that level. The statement that the older sibling, in contrast to the younger one, "behaved as a female since early childhood", raises the question whether the systemic androgen level influencing the sexual differentiation/masculinization o during its hormone-sensi of prenatal development in this sibling than in th one. Mammalian researcl vided ample evidence that and duration of androger during the homone-sensit perinatal period of brair ment affect later behavioi linization. This principle apply to humans as well. R my team in 46,XX indivi 21-OHD CAH has clearl dose-response relationshi drome severity (which is with the degree of androg with gender-related behav and related research in l human primates and hum it likely that these GR effe marily prenatal rather tha tal in origin.[5,6] However, early critical period of gen entiation, the hormone-se riod of sexual differentiat brain is much longer and e into the second half of pre

Our studies show co variability of GR in i with a given degree of CA ity, as one also sees it in no males and females, so tha androgen production is not the only biological f explains interindividual d in behavioral masculiniz addition, one has to consic tial variations in systemic metabolism, e.g., by aroma or in androgen utilization drogen receptor modulatic nucleotide repeats in the receptor gene,[8] also the p of CNS-limited variations crine processes such as pr of neurosteroids and the steroid co-activators and c tors,[9,10] and last but not le tributions from non-steroi genetic effects on temperar

Although psychosocia

contribute to GR,[12] the markedly masculinized GR of 21-OHD CAH girls appears to be rather unresponsive to parental gender-normalizing pressure,[13] and recognition of children's gender by their peers is not primarily based on genital status.[12] However, gender-related behaviors and interests that are atypical for the assigned gender are salient among the commonly given reasons for gender dysphoria and patient-desired gender-change by both intersex and transsexual patients in later adolescence and adulthood. On the other hand, core GI as male or female can accommodate considerable variations of GR, and my own team's research has shown a lack of correlation of GI and GR in 21-OHD girls,[14] which makes it unlikely that the processes underlying the development of GI and GR are identical. Many individuals with a marked degree of gender-atypical GR do not suffer from gender dysphoria, while others with a similar degree do, and we still cannot pinpoint the etiological difference. Overall, it currently appears more likely that it is the confluence of a variety of interacting biological, social, and psychological factors rather than one prominent factor among these that pushes a given child or adolescent towards gender dysphoria or actual gender-reassignment. Thus, when deciding for the newborn with a disorder of sex development on the gender assignment with optimal prognosis for stable GI development, we need to consider whether and to what extent the genital status at birth permits inferences on the androgenization of the brain, which varies considerably between syndromes, and to take into account all other known relevant factors including psychosocial and cultural ones. In cases of potential gender re-assignment after infancy, a comprehensive evaluation of the patient's gender status (GR, GI, and any indications of gender dysphoria) must be added.

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Medical chaperoning at a tertiary care hospital in Saudi Arabia: Prevalence and patient preference

To the Editor: The prevalence of medical chaperoning and the related patient preference in Saudi Arabia (or other Islamic/Arab countries) have not been well documented. We examined these issues in the out-patient clinics of a tertiary care hospital in Riyadh, Saudi Arabia, using a questionnaire that was completed during a personal interview. The study protocol, including verbal consent, was approved by the Research Ethics Committee of the institution. Two hundred thirty-nine patients were approached and 224 (94%) agreed to participate (15 declined for undeclared reasons).

Two hundred and five participants (2 males and 203 females, 92%) were seen by a physician of the opposite gender; 78 (38%) and 53 (26%) of which did not have a chaperone during the current medical interview and exam, respectively. When not present, a chaperone was rarely offered by medical staff (2%) and never requested by the patient. Of the 224 participants, 72 (32%) and 48 (21%) recalled that a chaperone was absent during previous medical interviews and exams, respectively. Table 1 shows chaperoning according to types of clinic and medical encounter. A significant association was found between the presence of a chaperone and clinic types for both interview and exam. There was also a significant association between the presence of a chaperone and types of medical encounter for all clinics ($P<0.0001$)

Table 1. Chaperoning according to types of clinic and medical encounter.

Clinic	Interview Number (%)		Exam Number (%)	
	Yes	No	Yes	No
Cardiovascular	20 (61)	13 (39)*	26 (79)	7 (21)*
Family Medicine & Polyclinics	10 (24)	32 (76)*	11 (26)	31 (74)*
Medicine	32 (78)	9 (22)*	29 (71)	12 (29)*
Neurosciences	19 (79)	5 (21)*	24 (100)	0 (0)*
Obstetrics & Gynecology	8 (47)	9 (53)*	16 (94)	1 (5.9)*
Surgery	14 (64)	8 (36)*	21 (96)	1 (4.5)*
Oncology	17 (90)	2 (11)	18 (95)	1 (5.3)*
Orthopedic Surgery	5 (100)	0 (0)	5 (100)	0 (0)
Kidney Transplant	2 (100)	0 (0)	2 (100)	0 (0)

*The *P* value of Fisher's exact test for the association of chaperone presence and types of clinic is $P < 0.0001$ for both interview and exam.

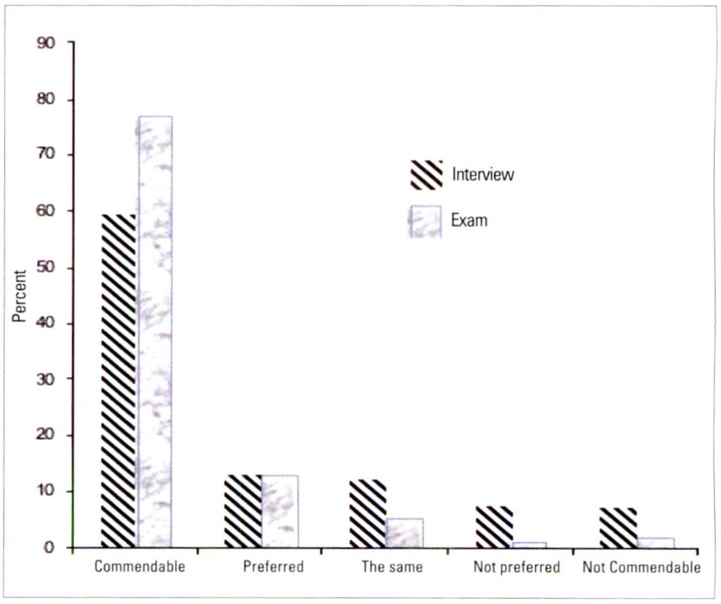

Figure 1. Patient's view of chaperoning during medical encounter.

and in the case of Family Medicine and Polyclinics ($P<0.0001$). Of the 78 participants interviewed by a physician of the opposite gender in the absence of a chaperone, 77 (99%) were not offered a chaperone by the hospital staff and none requested one. Similarly, of the 53 participants examined by a physician of the opposite gender in the absence of a chaperone, 52 (98%) were not offered a chaperone and none requested one.

Ninety-one percent of chaperones during an interview were patient relatives. Relatives and staff nurses contributed equally during an exam (38% and 39%, respectively). Fifty-six percent and 21% of chaperones during an interview or exam, respectively, were males.

Figure 1 depicts the preference of the 224 participants regarding chaperoning. Fifty-one percent and 85%, respectively, of the participants who did not have a chaperone viewed the presence of a chaperone as commendable/preferred during interview and exam. The reasons most commonly cited for preferring a chaperone during an interview/ exam were religious (53%/ 63%), psychological (50%/ 49%), and social (22%/ 25%) and for preferring not to have one were psychological (58%/ 38%) and privacy and confidentiality (52%/ 63%). The prevalence of chaperoning in our study (62% during an interview and 74% during an exam) is consistent with the results of previously reported studies in other parts of the world, which were mostly physician-based rather than patient-based.[1-3]

In contrast to previous reports,[1-3] we found that family members comprised the majority of chaperones. This could be due to inadequate nursing staff or to the social norm that most female patients are usually accompanied by family members. Compared to previous reports,[4-6] our study showed a higher rate of patient preference for chaperoning, which is likely related to different social norms and religious values. Given this degree of preference, our observation that the patients who had a medical encounter without a chaperone were rarely offered a chaperone and never asked for one raises concerns about the training of hospital staff and the knowledge of patients about their rights. The results of the study may not be generalizable to all patients in Saudi Arabia. We studied only outpatient clinics in one hospital. Further, although we aimed to study both male and female patients, our participants were 97% females.

Several bodies have developed guidelines and policies for chaperoning.[7-9] The standards of practice regarding chaperoning at KFSH&RC are not clearly stated. Since there is a strong patient preference to have a chaperone during medical encounters, clear policies and guidelines should be developed and more resources should be allocated to educate both patients and hospital staff on patient rights. Further studies in other hospitals in Saudi Arabia will assist in determining the overall degree of deficiency in chaperoning as well as the preferences of patients and may help set national guidelines.

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Arab and Muslim Physicians and Scholars

Abu Al Qasim Al Zahrawi (Albucasis): Pioneer of Modern Surgery

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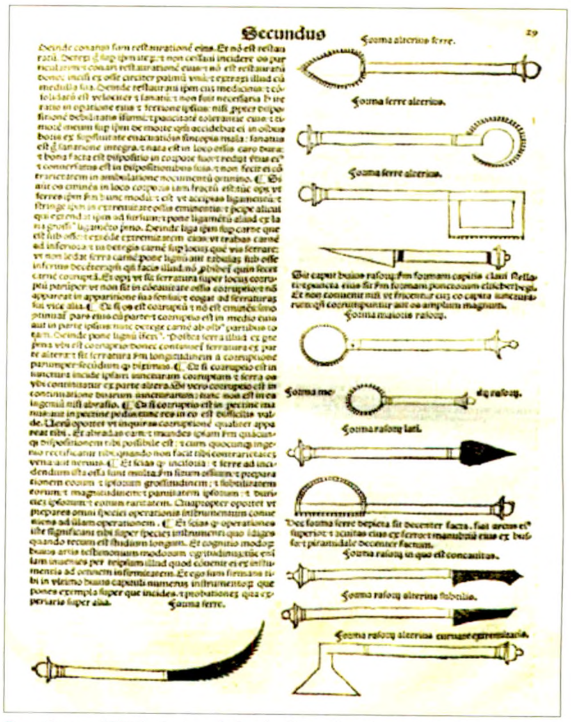
Abu Qasim Khalaf Ibn Abbas Al Zahrawi, known in the West as Albucasis or Zahravius, was born in 936 AD in Al-Zahra', a suburb, six miles northwest of Cordoba, the capital of Muslim Spain (Al-Andalus). His ancestors were from the Al Ansar tribes of Al Madina Al Munawwarah who came from the Arabian peninsula with the Muslim armies which conquered and lived in Spain. Al-Zahrawi traveled rarely, and spent most of his life in his hometown as a practicing physician-pharmacist-surgeon.[1]

He served as the court physician to Caliph Al-Hakam-II, at a period considered as the "Golden Age" of Arab Spain when natural and mathematical sciences reached their peak. After a long and distinguished medical career, he died in 1013 AD at the age of 77.

Around the year 1000 AD, he wrote his famous book "*Al Tasreef Liman 'Ajaz 'Aan Al-Taleef*", (The Clearance of Medical Science For Those Who Can Not Compile It). It was a summation of about fifty years of medical education, training, practice and experience. The thirty volumes of the medical encyclopedia covered various aspects of medical knowledge. In addition to sections on medicine and surgery, there were sections on midwifery, pharmacology, therapeutics, dietitics, psychotherapy, weighs and measures, and medical chemistry.[1]

In *Al-Tasreef*, three chapters were devoted to surgery. Some of the procedures and techniques detailed in these chapters include the following:

- Surgery of the eye, ear, and throat. He fully de scribed tonsillectomy and tracheostomy.
- He devised instruments for internal examination of the ear.
- He devised an instrument used to remove or insert objects into the throat.
- He described how to use a hook to remove a polyp from the nose.
- He described the exposure and division of the temporal artery to relieve certain types of headaches.
- He utilized cauterization, usually to treat skin tumors or open abscesses. He applied cauterization procedure to as many as 50 different operations.
- Application of ligature for bleeding vessels and internal stitching utilizing catgut. He preceded the famous French military surgeon Ambroise Pare (1510-1590), claimed to be the first European to utilize sutures, by five centuries.
- Treatment for anal fistulas.
- Setting dislocated bones and fractures. His method for setting and reducing a dislocated shoulder was centuries before Kocher introduced his similar technique to European medicine.
- Removal of urinary bladder calculi. He advised that the treating physician has to insert a finger into the rectum of the patient, move the stone down to the neck of



Page from a 1531 Latin translation by Peter Argellata of Al Zahrawi's treatise on surgical and medical instruments.

the bladder, then make an incision in the rectal wall or the perineum and remove the stone.

- He devised instruments for inspection of the urethra.
- He is credited to be the first to describe ectopic pregnancy.
- He devised several dental devices and artificial teeth made of animal bones.

Al Zahrawi is considered the father of operative surgery.[2,3] He is credited with performance of the first thyroidectomy.[4] The last chapter of his comprehensive book, named "On Surgery", was dedicated to surgical instruments. He introduced over 200 surgical tools, a staggering number by all standards. He gave detailed descriptions of for using probes, surgical knives, scalples, and hooks. He also devised and invented surgical scissors, grasping forceps and obstetrical forceps. His illustrations of surgical instruments were the earliest intended for use in teaching and in methods of manufacturing them.[1]

Abdel-Halim et al gave a detailed study of Al Zahrawi's technique of cystolithotomy after inventing operative instruments not known in the Greco-Roman era.[5] They reviewed his operative technique in women, his recommendations of two -stage operation in complicated cases and his contributions to lithotripsy by introducing a crushing forceps (Al-Kalaleeb forceps) and a driller fragmenting forceps (Al-Mishaab) to remove impacted stones.[5]

Al Zahrawi contributed early descriptions of neurosurgical diagnoses and treatment including management of head injuries, skull fractures, spinal injuries and dislocations, hydrocephalus, subdural effusions, headache and many other conditions.[6] He described vividly a case of hydrocephalus due to congenital defect of drainage of cerebrospinal fluid: "I have seen a baby boy whose head was abnormally enlarged with prominence of the forehead and sides to the point that the body became unable to hold it up".[1]

In addition, he made significant contributions to pediatric surgery. In addition to his description of hydrocephalus, he described harelip, adenoids, ranula, imperforated external urinary meatus, perforated anus, hermaphrodites, gynecomastia, supernumerary and webbed fingers.[7] He was the first to describe in detail the medical aspects of hemophilia.

His medical writings were highly regarded in the West particularly after being translated by Gerard of Cremona, Rogerius Frugardi, Ronaldus Parmensis and others. His surgical teachings were the most advanced in the Middle Ages until the thirteenth century.[1]

Al-Tasreef was an essential component of the medical curriculum in European countries for many centuries.[8] The famous French surgeon Guy de Chauliac (1300-1368) quoted him over 200 times in his book appended its Latin edition to his own book on surgery. Several editions of this book (surgical chapters) were published including one at Venice (1497), at Basel (1541) and at Oxford (1778).

Finally, he emphasized child education and behavior, school curriculum and academic specialization. He advised that gifted and intelligent students be encouraged to study medicine after completing their primary education in language, grammar, mathematics, astronomy and philosophy.[1] This article is just a glimpse of the medical and surgical contributions of this great Arab physician from Andalus to the world.

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Heck's disease

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Ann Saudi Med 2007; 27(3): 222

A 7-year-old girl presented with a 10-month history of the development of multiple, non-tender, sessile, soft papules, plaques, and nodules with a flat-topped, pink to pale, grainy surface on her oral mucosa. She was otherwise completely healthy. Her family history was nonsignificant. She was diagnosed with Heck's disease, also known as focal epithelial hyperplasia, a benign condition of the oral cavity that has a predilection for native Indians from North and South America, Eskimos, and South Africans of Khoi-Shan extraction. There is a strong association with HPV types 13 and 32, which are found in over 90% of biopsied lesions.[1,2] In addition, a genetic predisposition and an immunocompromised host status, due to malnutrition and crowded living conditions, are thought to be contributing factors. Focal epithelial hyperplasia shows a female predilection and is typically observed in the first two decades of life.[1,3] Clinically, the disease is characterized by multiple, non-tender, sessile, soft papules, plaques, and nodules with a flat-topped, pink to pale, grainy surface. Diffuse, multifocal mucosal involvement of the labial and buccal mucosa and lateral tongue is the classic presentation. Although papulonodular eruption is the most common presentation, a papillomatous pattern with a pale or white surface may be observed on the lateral tongue and buccal mucosa.[1] The lesions of focal epithelial hyperplasia spontaneously resolve in some patients within a few months to several years. Conservative surgical excision may be performed for aesthetic or functional purposes. Other treatment modalities with variable effectiveness have included cryotherapy, carbon dioxide laser ablation, topical application of 25% podophyllin resin, and vitamin therapy.[4] Recurrence of these oral lesions, even following spontaneous regression, is not uncommon.

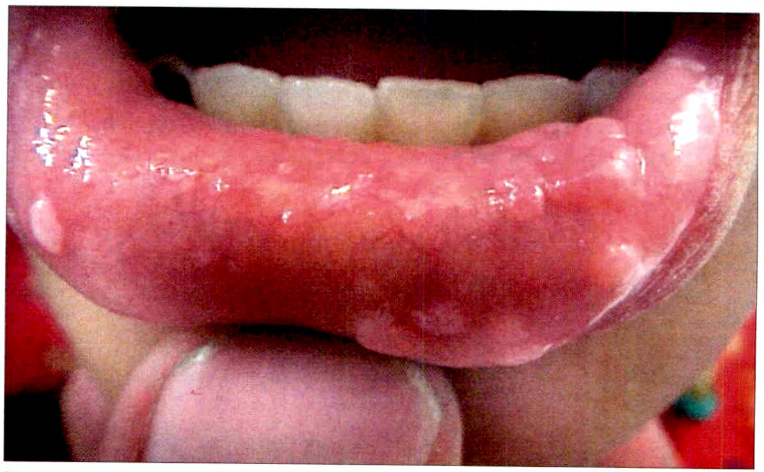

Figure 1. Papules, plaques and nodules indicative of Heck's disease in a 7-year-old girl.

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what's your diagnosis?

Diagnosis: Brugada Syndrome

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We describe a 29-year-old man who presented to our emergency department (ED) with chest pain and features of Brugada syndrome on ECG, but the diagnosis was only made after his third visit to the ED. It is important to shed the light on this rare but important syndrome since it affects young people and when diagnosed, treatment options to prevent sudden cardiac death are highly successful.

Brugada syndrome is one of the causes of sudden cardiac death in the young with no structural heart abnormalities. The current prevalence is estimated to be 0.4% to 0.6% in western countries, but a higher frequency may be found in Far East countries like Thailand.[1,2] The syndrome has a characteristic pattern on resting ECG, but some times a provocative test needs to be done to demonstrate the abnormality.

First described by Pedro and Joseph Brugada in 1992, Brugada syndrome is an autosomally dominant inherited cardiac disease with variable expression, resulting from mutation in the SCN5A gene, causing life-threatening polymorphic ventricular arrhythmia in a patient who is otherwise healthy. Men are more commonly affected than women. Sudden death happens usually while sleeping and is the presenting symptom of one third of patients, and is not related to exercise.[3] The

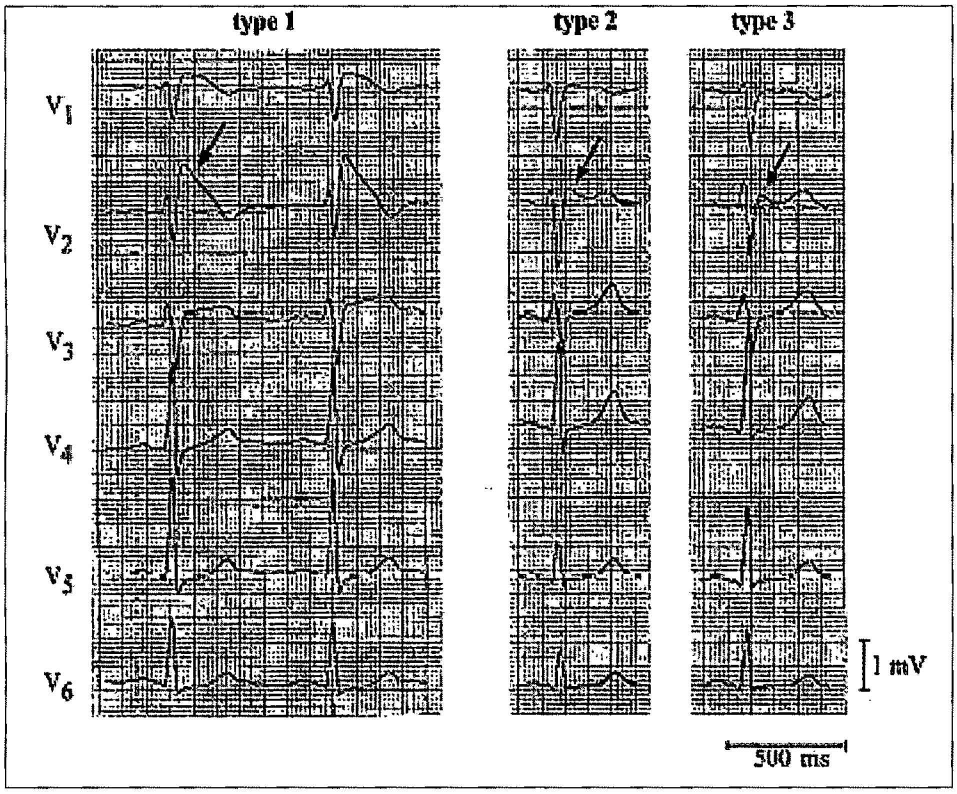

Figure 2. Precordial leads of patients with Brugada syndrome showing all three patterns. From Wilde, AA Eur Heart J 2002; 23: 1648, with permission.

major pathophysiologic mechanism is loss of sodium channel function.

Brugada syndrome has a characteristic ECG pattern in the form of incomplete RBBB and ST segment elevation in the right precordial leads (V1 to V3), thought to be due to an alteration in the action potential in the epicardial but not the endocardial cells. The ECG changes may be dynamic and have transient normalization. Three different patterns of ST elevation have been described; in the classic Brugada ECG (type 1), the elevated ST segment (≥ 2 mm) descends with an upward convexity to an inverted T wave (Figure 1). Type 2 and 3 patterns have a " saddle back" ST-T wave configuration in which the elevated ST segment descends toward the baseline, then rises again to an upright or biphasic T wave. The terminal part of the ST is elevated ≥1 mm in type 2 and < 1 mm in type 3 (Figure 2).[3,4]

Diagnosis of Brugada syndrome should be suspected in patients with ST segment elevation in more than one right precordial lead (V1-V3) and one of the following:[4] syncope, a family history of sudden cardiac death at an age younger than 45 years, typical ST segment changes in family members, nocturnal agonal breathing, documented ventricular fibrillation, or electrophysiological inducibility. The appearance of typical ECG changes alone in the absence of one of the above mentioned criteria is considered to represent an idiopathic Brugada ECG pattern but not the Brugade syndrome. In those with normal or transient ECG changes, the characteristic changes can be provoked by administration of sodium channel blockers, like flecainide or procainamide.[3]

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Recognizing parents' influence not only in families but beyond into community groups, this year's World Heart Day, 30th September 2007, is themed "*Team Up for Healthy Hearts*". World Heart Day activities include health checks, organized walks, runs and fitness sessions, public talks, stage shows, scientific forums, exhibitions, concerts, carnivals, and sports tournaments.

World Heart Day, now in its eighth year, is run by the World Heart Federation's member organizations in over 100 countries. The World Heart Federation is a nongovernmental organization based in Geneva, Switzerland, committed to helping the global population achieve a longer and better life through prevention and control of heart disease and stroke.

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ORTHOKIDS

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06-07 November 2007 ● 25-26 Shawwal 1428

Workshop by Department; 08 November 2007 / 27 Shawal 1428

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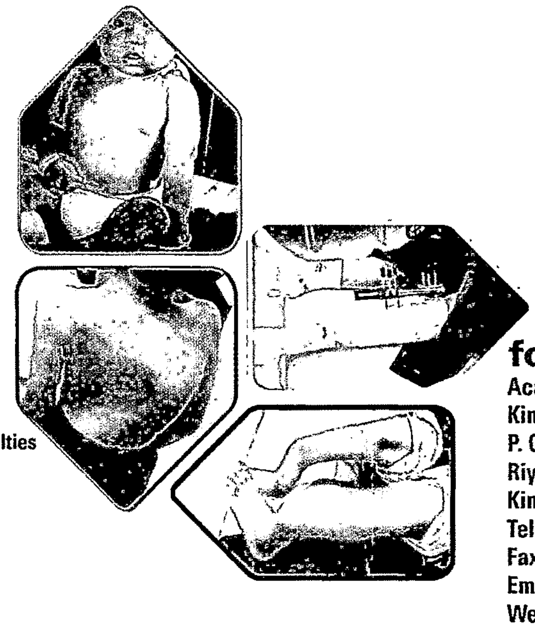

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for more information:

Academic and Training Affairs, CME Section
King Faisal Specialist Hospital and Research Cent
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Kingdom of Saudi Arabia
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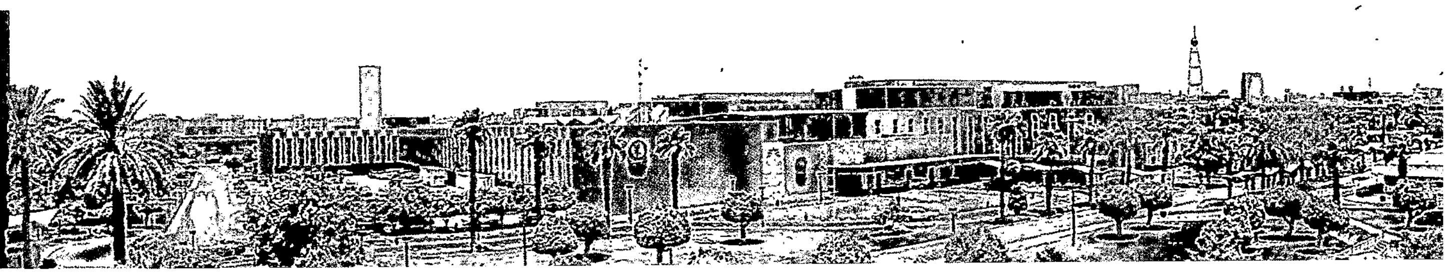
VENUE



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	Pediatric Radiology
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	Endocrine & Breast Surgery
	Pediatric Surgery *
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First Announcement

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Published by the King Faisal Cancer
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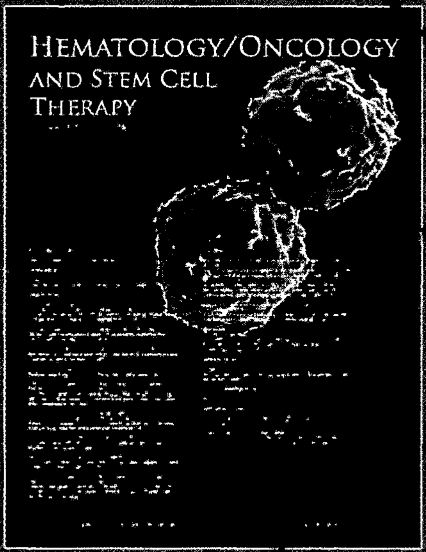
First Issue January 2008



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- Genitourinary Cancer
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- Head & Neck Cancer
- Hemoglobinopathies
- Lymphoid Malignancies
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- Myelodysplastic Syndrome
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تقدير وزن الجنين بتخطيط الصدى باستخدام طول عظم الفخذ: معادلة هونارفر

المقدمة: يحدث نمو الجنين نتيجة تفاعل عوامل متنوعة ويمكن تقديره بمقاييس الموجات فوق الصوتية. يعد طول عظم فخذ الجنين مقياساً لتقدير وزن الجنين وفقاً للفئة العرقية للفرد إذ تتفاوت أنماط نمو الجنين بين الأعراق المختلفة.

المرضى والطرق: شملت هذه الدراسة المستقبلية ٥٠٠ سيدة حامل في الأسبوع ٣٦ من الحمل. أجري تخطيط لصدى في الزمن الحقيقي لقياس طول عظم الفخذ ثم وزن الجنين والذي تم تقديره باستخدام معادلة هونارفر الثانية. تم اختبار الارتباط بين الوزن ا المقدر للجنين والوزن الحقيقي بمعامل ارتباط بيرسون وعلاقتها بالعمر ومعدل كتلة الجسم عند الأم وجنس الوليد والإنجابية باستخدام اختبار التراجع المتعدد.

النتائج: ترابط وزن الجنين المقدر بمعادلة هونارفر بوضوح مع الوزن الحقيقي للطفل ووزن الولادة الفعلي. بناء عليه، تعتبر هذه المعادلة صحيحة لتقدير وزن الجنين فضلاً عن كونها لم تعتمد على العمر أو معدل كتلة الجسم عند الأم، أو على جنس الجنين أو إنجابية الأم.

الاستنتاج: يلعب الاستعداد العرقي دوراً هاماً في تقدير وزن الجنين. أعطت طريقة هونارفر التقدير الأفضل لوزن الولادة الفعلي لدى المواليد الإيرانيين ويوصى باعتمادها.

الارتفاع المفرط في سرعة تثفل الكريات الحمراء عند الأطفال

المقدمة: يرتبط الارتفاع المفرط في سرعة تثفل الكريات الجمراء (mm/hr ESR ≥ ١٠٠) عادةً بأمراض هامة. أجريت هذه الدراسة لتقييم أهمية ذلك على المرضى من الأطفال في مستشفى عسير المركزي.

المرضى والطرق: تمت مراجعة جميع فحوص سرعة تثفل كريات الدم الحمراء التي أجريت للأطفال في الفترة ما بين سبتمبر ٢٠٠١م و ديسمبر ٢٠٠٢م. كما تمت دراسة السجلات الطبية للمصابين بارتفاع مفرط في سرعة تثفل الكريات الحمراء (mm/hr ESR ≥ ١٠٠) (الفئة ١) من ناحية العمر والجنس والتشخيص ومقدار سرعة التثفل ومستوى الهيموجلوبين وعد الخلايا البيضاء. توزع التشخيص على سبعة أبواب: الخباثة، ومرض النسيج الضام، وأمراض المناطق الحارة، والعدوى الخفيفة، والتهابات الشديدة، وأمراض الكلى وأخرى متنوعة. تم اختيار ١٤٥ مريضاً لديهم سرعة تثفل أدنى من ١٠٠ ملمتر (الفئة ٢) عشوائياً للمقارنة.

النتائج: من بين ٢٥٤٠ مريضاً لديهم زيادة في تثفل الكريات الحمراء كان لدى ٩٩ منهم زيادة مفرطة فوق ١٠٠ ملمتر (٣,٩٪). توزع المرضى على ٥٤ من الذكور و٤٥ من الإناث وتراوح متوسط العمر بين ٤٨,٢±٧٢ شهراً. كان السبب الأكثر شيوعاً هو العدوى (٤٩,٥٪) يليه مرض النسيج الضام (٢٦,٣٪)، فالخباثة (١٢,١٪)، ثم أمراض الكلى (٨,١٪). ارتبطت الخباثة بتدني مستوى الهيموجلوبين (٨,٢ جم/ديسلتر). أظهرت المقارنة بين الفئة ١ والفئة ٢ مع الأخذ في الاعتبار باب التشخيص لكل على حدة أن متوسط عد الخلايا البيضاء أعلى لدى مرضى الفئة ١ المصابين بعدوى خفيفة. كما أن مستوى الهموجلوبين لدى مرضى الفئة ١ المصابين بمرض النسيج الضام أدنى وبدرجة ملحوظة عن مرضى الفئة ٢ المصابين بالمرض ذاته دون فروق مهمة بين أبواب التشخيص الأخرى.

الاستنتاج: السبب الأكثر شيوعاً للارتفاع المفرط في سرعة تثفل الكريات الحمراء هو العدوى. يمكن أن يستخدم هذا الارتفاع المفرط كمؤشر على المرض لكن ليس كأداة للكشف عن أي مرض.

الخلاصات العربية

نتائج علاج السل في مراكز الرعاية المتخصصة

مقدمة: لم توثق نتائج العلاج الكيميائي للسل الرئوي والسل غير الرئوي والسل المنتشر بشكل جيد وبخاصة في الدول النامية. قامت هذه الدراسة بتقييم نتائج علاج السل ونسبة الشفاء إلى العلاج والوفيات بين المرضى المصابين بجميع أنواع السل في مركز رعاية متخصص بالسعودية.

المرضى والطرق: شملت الدراسة جميع الحالات التي شخصت وعولجت من المتفطرة السلية النشطة بين العامين ١٩٩١م و٢٠٠٠م. شملت البيانات التي تم جمعها نوع الإصابة السلية ونتائج العلاج والانتكاسة والمرضيات.

النتائج: تم تشخيص وعلاج ٥٣٥ حالة سل على مدى عشر سنوات. وتم التحقق من السل الرئوي في ١٤١ حالة. (٢٦,٤٪). والسل غير الرئوي في ٣٣٩ حالة (٦٣,٣٪). والسل المضاعف (الرئوي وغير الرئوي) في ٥٥ حالة (١٠,٣٪). وجدنا مراضة مصاحبة في ٢٧٧ مريضاً (٥٢٪). وتم الكشف عن ضعف المناعة لدى ١٨١ مريضاً. (٣٤٪). كانت نسبة الشفاء ٨٢٪. كانت نسبة الشفاء إلى العلاج ٨٦٪ في حالات السل غير الرئوي، ٧٨٪ في حالات السل الرئوي، و٦٥٪ في حالات السل المنتشر. كانت نسبة الوفيات هي ١٨٪. كانت أعلى نسبة وفيات في حالات السل المنتشر (٣٤,٩٪). تليها حالات السل الرئوي (٢١,٨٪) ثم حالات السل غير الرئوي (١٣,٦٪). كانت ٤٧٪ من الوفيات ذات علاقة مباشرة بالسل. حدثت انتكاسة لدى ١٤ مريض من أصل ٣٤٩ مريض (٤٪) بعد ٢٤ شهر من المتابعة.

الخاتمة: على الرغم من الرعاية المتخصصة نجد أن حالات السل المضاعفة تؤدي إلى نسبة عالية من الوفيات. التشخيص الأبكر والعلاج الكيميائي الملائم والتام أمران مهمان لتحسين النتائج.

تقييم سكر الدم لدى مرضى السكري من النوع الأول باستخدام جهاز الديلزة الدقيقة لقياس الجلوكوز المستمر

مقدمة: تقوم أجهزة القياس المستمر للجلوكوز بمراقبة التغيرات في تركيز الجلوكوز بالدم لحظة بلحظة، وذلك ما لا يمكن كشفه بالمتابعة الشخصية المتقطعة. قد تؤدي أجهزة القياس المستمر إلى التحسن في ضبط سكر الدم. وقد قمنا بتقييم طريقة الديلزة الدقيقة لتحسين السيطرة على سكرية الدم لدى مرضى السكري من النوع الأول والذين يتلقون العلاج بأساليب مختلفة من إعاضة الأنسولين الأساسي.

المرضى والطرق: تم تقسيم ٥٢ مريضاً بالسكري من النوع الأول قيد العلاج بـ (NPH) مرتين يومياً وأنسولين أسبارت قبل الوجبات تقسيماً عشوائياً على فئتين: الفئة الأولى بالاستمرار على (n=٢٦) (NPH) أو (الفئة الثانية) "جلرجين" مرة واحدة يومياً (n=٢٦) وتم البدء بنظام تسجيل يومي للجلوكوز عند البداية وبعد أربعة أشهر.

النتائج: في البداية كان الوقت الذي فيه سكر الدم في حد السواء (الجلوكوز بين ٣,٩ و ٨,٠ مليمول/لتر) هو ٣٧,٩٦ + ٦,٨١٪ لفئة (NPH) و ٣٥,٨٣ + ٦,٢٤٪ لمجموعة "جلرجين". أما في نهاية الفترة فقد ازداد الوقت الذي يكون فيه سكر الدم سوياً لدى الفئتين على التوالي (٥١,٠٢ + ٧,٢٢٪ و ٥٧,٢٩ + ١٠,٢٧٪ ، ٠,٠٠١› P مقارنة بما قبل العلاج). كما أنه في البداية كانت الفترة التي كان فيها سكر الدم في حدود منخفضة (جلوكوز ‹ ٣,٩ مليمول/لتر) هي ٩,٩٨ + ٢,٥٧٪ للفئة الأولى و ١٠,٢٤ + ٣,٥٥٪ للفئة الثانية). أما في النهاية فقد تناقصت فترة هبوط السكر في الفئتين (٨,٠٠ + ٢,١٣٪ و ٦,٥٩ + ٢,٠٤٪، ٠,٠٠١›P مقارنة بما قبل العلاج للفئتين).

الخاتمة: أعطى تحليل البيانات معلومات عن سكر الدم أكثر من (HbA١C) و المتابعة الشخصية لسكر الدم وأظهر غياب أثر ذروة الفعالية وقلة النسبة المئوية للفترة التي ينقص فيها سكر الدم إلى المدى المنخفض لدى فئة "جلرجين"

الخلاصات العربية

داء الصفر المراري: دور التصوير بالموجات فوق الصوتية في التشخيص والعلاج

مقدمة: تكون الطرق التقليدية للتصوير الإشعاعي في كثير من الأحيان غير فعالة للتعرف على الديدان في المسالك المرارية. أما التصوير بالموجات فوق الصوتية فهو طريقة آمنة وسريعة وغير باضعة ومعروفة بدقتها التشخيصية. درسنا مظاهر داء الصفر المراري في صور الموجات فوق الصوتية ودور التصوير بالموجات فوق الصوتية في التشخيص والعلاج.

المرضى والطرق: في دراسة استباقية على مدى ٥ سنوات تم تشخيص داء الصفر المراري لدى ٤٦ مريضاً يمنياً بواسطة الموجات فوق الصوتية. استند التشخيص بصفة رئيسية على مظهر صورة الموجات فوق الصوتية مدعومة بالنتائج السريرية والمخبرية وأثبت بنتيجة العلاج الجراحي أو الطبي أو الخروج التلقائي للديدان. أجري تصوير متابعة بالموجات فوق الصوتية لتأكيد التشخيص ومراقبة العلاج.

النتائج: كانت الطفيليات موجودة في القناة المرارية الرئيسية المتوسعة لدى ٢٣ مريضاً، وفي المرارة لدى ١٢ مريضاً، وفي القنوات داخل الكبد لدى ٦ مرضى، وفي القناة البنكرياسية الرئيسية لدى ٤ مرضى وبشكل خراج داخل الكبد لدى مريض واحد. كان منظر الصفر الخراطيني بشكل شرائح خطية أو منحنية مولدة للصدى لا تلقي بظلال، مفردة أو متعددة، مع أو بدون خطوط مركزية أنبوبية صدوية تمثل المسالك الهضمية للدودة. شوهد منظر شبيه بالمعكرونة لدى ٩ مرضى، وشدف عديمة الشكل لدى مريضين. أجريت عملية جراحية لستة عشر (١٦) مريضاً، وعولج ٢٠ مريضاً طبياً (بما في ذلك الخروج التلقائي للدودة لدى ٧ مرضى بدون علاج) وأجري استخلاص للديدان باستخدام التصوير الراجع للأوعية المرارية والبنكرياس بالمنظار لدى عشرة مرضى.

الخاتمة: تبين أن تصوير المتابعة بالموجات فوق الصوتية فعال لتأكيد التشخيص ومراقبة العلاج.

الخلاصات العربية

معالجة الظفرة بالاستئصال البسيط وحده بالمقارنة مع الاستئصال البسيط مع قطرة ميتومايسين ج

مقدمة: الظفرة اضطراب عيني شائع في جميع أنحاء العالم. والهدف من هذه الدراسة هو تقييم فعالية الاستئصال البسيط وحده مع/أو بدون الميتومايسين الموضعي كعلاج للظفرة.

المرضى والطرق: أجريت هذه الدراسة على مرحلتين. في المرحلة الأولى، من ١٩٩١م إلى ١٩٩٤م، أجري استئصال بسيط لمائة (١٠٠) مريض (الفئة ١). في المرحلة الثانية، من ١٩٩٥م إلى ١٩٩٩م، عولج ٣٠٠ مريض (الفئة ٢) بنفس الطريقة زائد ميتومايسين موضعي (قطرة للعين ٠,٠٢٪ ٤ مرات في اليوم لمدة أربعة أيام بعد العملية). توبعت جميع الحالات لمدة ٥ سنوات. قورنت نسبة معاودة الظفرة لدى الفئتين.

النتائج: كانت متوسط عمر المشاركين ٤٩+١٣ سنة في الفئة ١ و ٤٧+١٧ في الفئة ٢. كانت الأعراض السريرية متشابهة لدى الفئتين (P>٠,٠٥) . شوهدت معاودة بعد سنة واحدة لدى ٢١ حالة (٢١٪) من الفئة ١، ولدى ٣ حالات (١٪) من الفئة ٢. بعد خمس سنوات كانت هناك معاودة لدى ٣١ حالة (٣١٪) في الفئة ١ و٣ حالات (١٪) في الفئة ٢ (P = ٠,٠٠٠١) . بالنسبة للمعاودة خلال خمس سنوات كان متوسط الزمن المنقضي قبل المعاودة لدى فئة الاستئصال البسيط ٣,٨٣ سنة (مدى الثقة ٩٥٪: ٣,٤٨ إلى ٤,١٧ سنة) و٤,٩٦ سنة لدى فئة الاستئصال البسيط مع ميتومايسين (مدى الثقة ٩٥٪: ٤,٩١ إلى ٥,٠ سنوات) (P<٠,٠٠٠١) .

الخاتمة: إن استعمال قطرة ميتومايسين ج مأمون على ما يبدو كعلاج للظفرة.

المدونـــات الطبيـــة السعوديـــة

السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصّصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول مكتب المطبوعات (ر.إ ٣٦).

سعر الاشتراك ١٠٠ ريال في السنة للأفراد داخل المملكة و٢٠٠ ريال في السنة للأفراد خارج المملكة و٥٠٠ ريال في السنة للمؤسسات. يمكن فتح اشتراك مجاني للأفراد و المؤسسات في الدول النامية.

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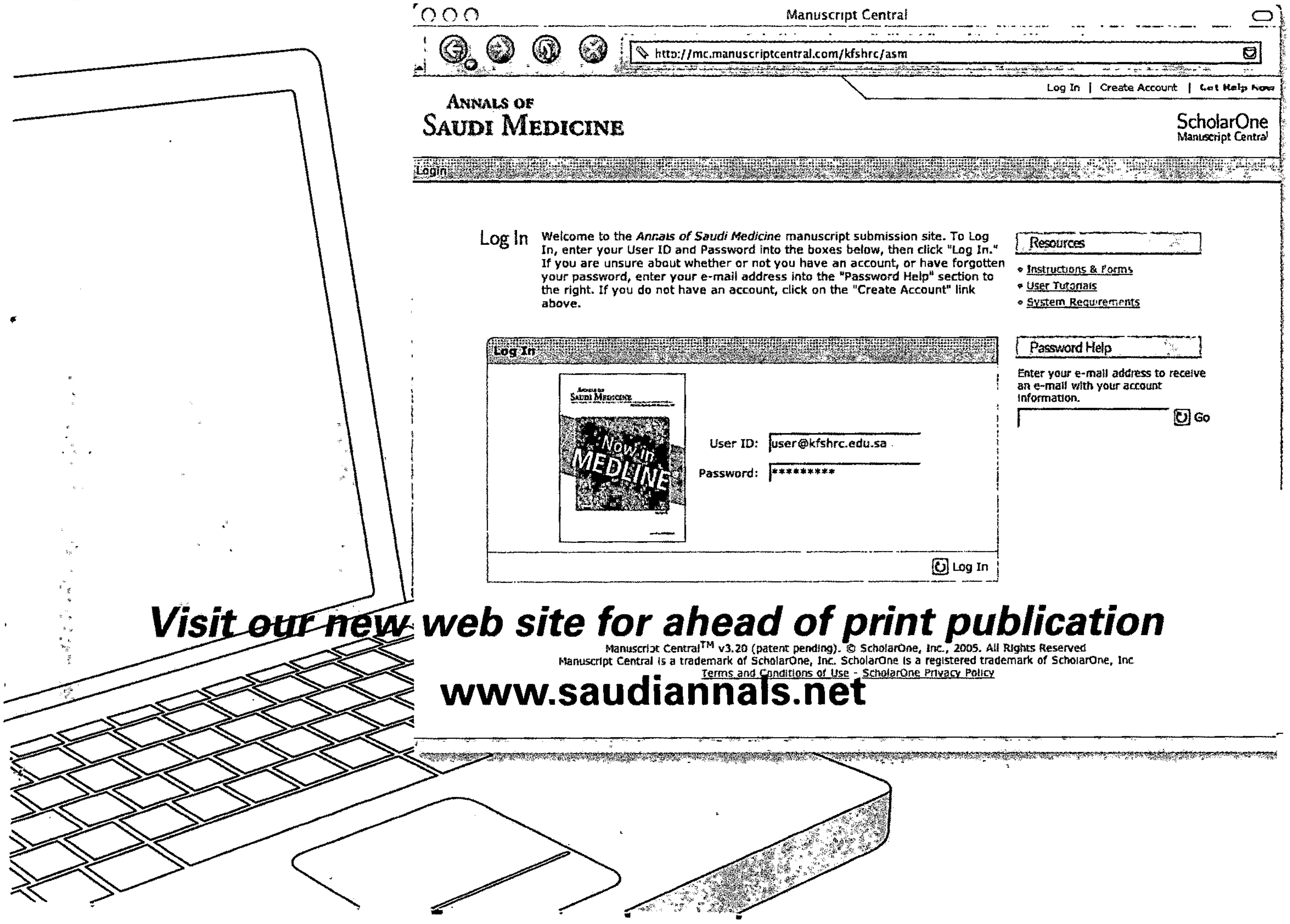

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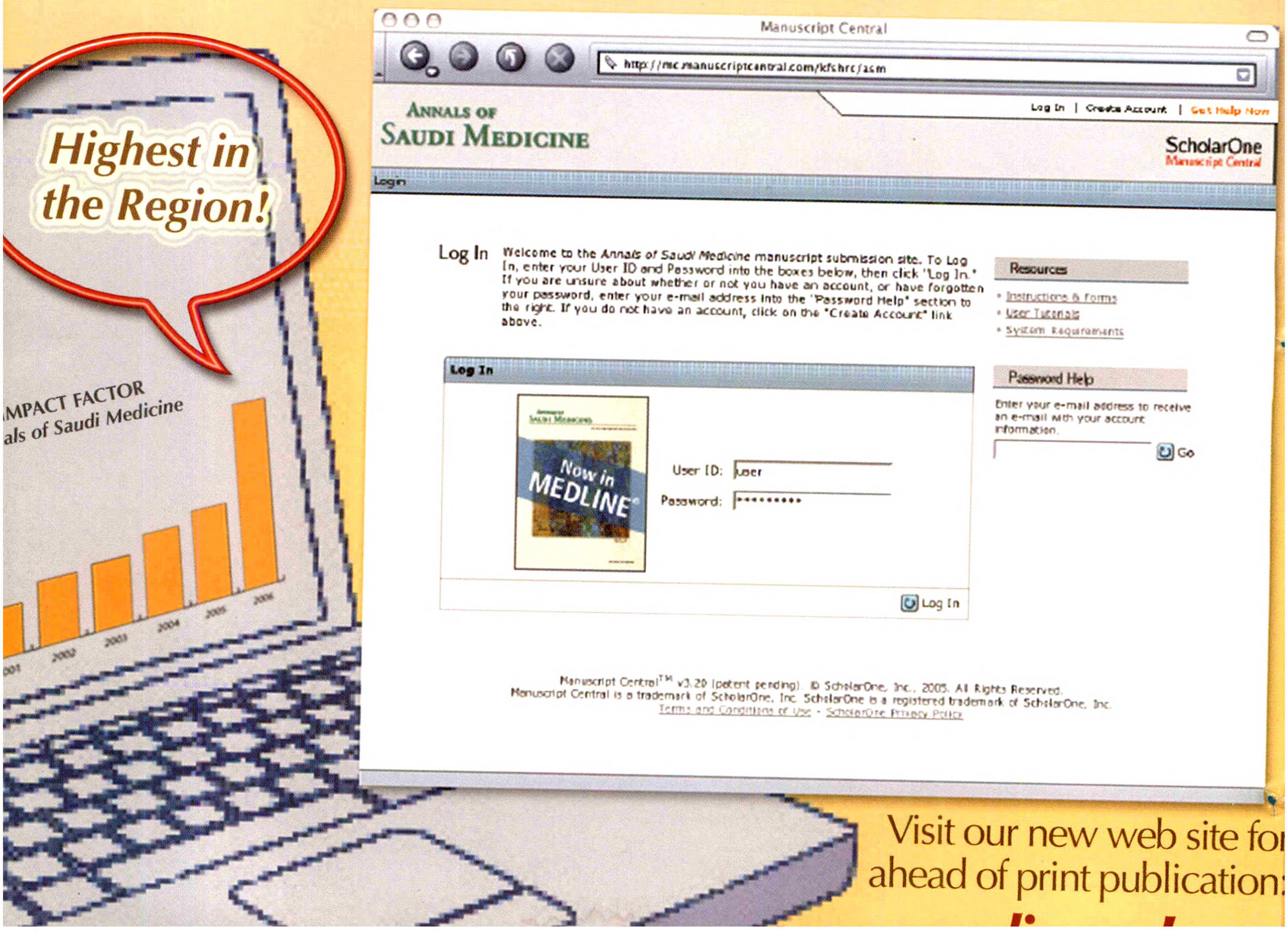

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OrthoKids International Symposium
06-07 November 2007/25-26 Shawwal 1428
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International Congress on Bone Marrow & Stem Cell Transplantation
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The 7th IEA-EMRO Scientific Meeting "Epidemiology: Translating Research to Health Care"
27-28 November 2007/17-18 Dhu Al Qada 1428

Advances in Diagnostic & Interventional Radiology
08-09 January 2008/ 29-30 Dhu Al Hijja 1428
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09 May 2007/22 Rabia Al Thani 1428

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01 November 2007/20 Shawwal 1428

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إعلان

يسر إدارة الإبتعاث والتدريب بالتعاون مع إدارة التمريض بمستشفى الملك فيصل التخصصي ومركز الأبحاث (مؤسسة عامة) أن تعلن عن رغبتها في إتاحة الفرصة للدراسة والتدريب في جامعة الملك سعود بن عبدا لعزيز للعلوم الصحية (كلية التمريض والعلوم الطبية المساعدة) للفتيات السعوديات والحصول على درجة البكالوريوس في علوم التمريض للفصل الدراسي القادم (**سبتمبر ٢٠٠٦**)

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- سعودية الجنسية
- حاصلة على مجموع لايقل عن ٨٠٪ في امتحان الثانوية العامة (**قسم علمي**)
- لايكون قد مضى على تخرجها اكثر من ٣ سنوات
- لايقل مجموع المواد العلمية واللغة الانجليزية عن ٨٥٪
- إجتياز الاختبار والمقابلة الشخصية المعد من قبل (**كلية التمريض والعلوم الطبية المساعدة)**
- تفرغ كامل للدراسة وان تكون لائقة جسدياً

المستندات المطلوبة:

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- شهادة الثانوية العامة الأصلية
- يشترط لمن حصلوا على الشهادة الثانوية من خارج المملكة معادلتها وتصديقها من وزارة التعليم العالي
- ٤ صور شمسية
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- خطاب بموافقة ولي الأمر بانضمام المتقدمة للدراسة في كلية التمريض والعلوم الطبية المساعدة.

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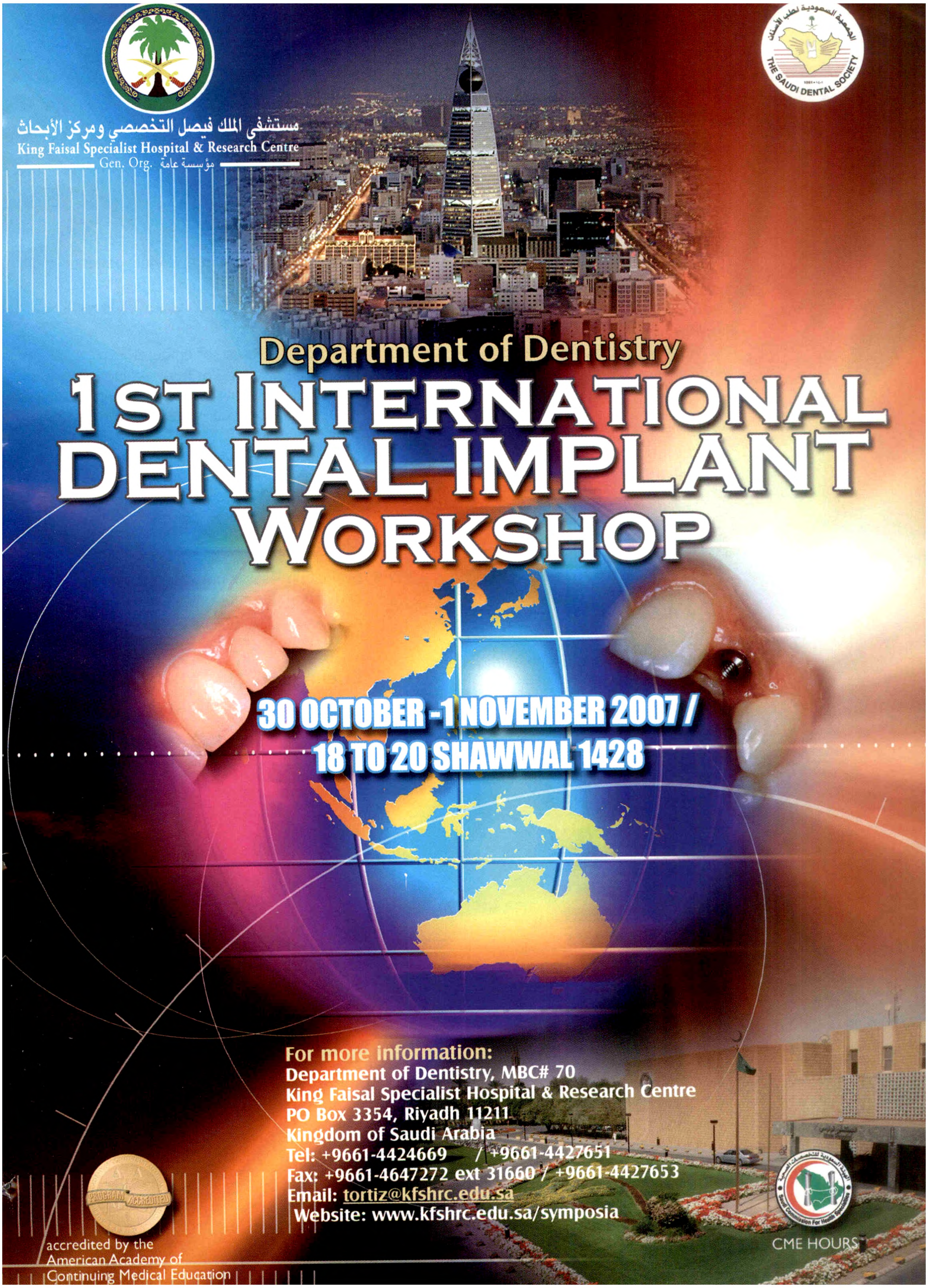

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summary of original articles

CANCER EPIDEMIOLOGY

Cancer incidence among the Bahraini population: a five-year (1998-2002) experience

Using data from the Bahrain Cancer Registry, Alsayyad and Hamadeh determined the epidemiological patterns of malignancies in Bahrain over a 5-year period and compared them with those of other Gulf Cooperation Council countries. They found 2405 cases of cancer in Bahrain over the 5-year period, with an annual average of 481 cases. The world age-standarized incidence rates (ASR) were 162.3 and 145.2 per 100 000 for Bahraini males and females, respectively. The most common cancer types for males were lung, bladder and prostate, while the most common types for women were breast, lung and ovary. Compared to other Gulf countries Bahrain had higher incidence rates for several types of cancer in both men and women. The rising trend in cancer incidence is likely to continue.

ALLERGY

Prevalence of airborne allergenic *Amaranthus viridis* pollen in seven different regions of Saudi Arabia

Hasnain and colleagues recorded the airborne incidence of *A. viridis* and other allergenic pollen in Al-Khobar, Dammam, Hail, Jeddah, Jizan, Qassim and Taif by samplers operated continuously for one year. *A. viridis*, which is known to be highly allergenic and a potential cause of respiratory allergic diseases, was a major component of outdoor airspora at all sites and the pollen was present throughout the year with distinct seasonal variations. Further studies are needed to confirm the allergenic impact of *A. viridis* pollen and sensitization of allergic individuals in Saudi Arabia.

PEDIATRIC NEUROLOGY

Primary congenital glaucoma in infants with abnormal brain MRI findings

MRI findings of the brain in infants with primary congenital glaucoma have not been reported in the literature. Dai and Saygili reviewed the records of 17 patients with PCG and analyzed MRIs of the brain and associated manifestations. Three of their patients had abnormal findings suggestive of agenesis of the corpus callosum. Two others had delayed myelinization. The results suggest a close relationship between PCG and delayed myelinization of the white matter, but more studies are needed to confirm these results.

PATHOLOGY AND GYNECOLOGICAL ONCOLOGY

Pattern of abnormal Pap smears in developing countries: A report from a large referral hospital in Saudi Arabia using the revised 2001 Bethesda System

Reports describing the frequency and pattern of abnormal Pap smears in developing countries using the revised Bethesda System are few. Abdullah reclassified all cervical Pap smears reported in the Pathology Department of King Abdulaziz Medical City, Jeddah, from the beginning of January 1998 to the end of August 2005, according to the revised system. Of 5590 sufficient smears, 261 (5%) were identified as abnormal and further classified. Although the study showed a lower incidence and wider age range of cervical epithelial cell abnormalities than others published internationally, the results emphasize the need for a well-organized cervical cancer screening program supplemented by larger national studies on the pattern of cervical abnormalities in Saudi Arabia.

PSYCHIATRY

Cognitive functions in euthymic patients with bipolar disorder

Ozdel and colleagues compared the cognitive performance of 27 bipolar euthymic patients with 21 healthy control subjects using tests of verbal and visual memory performance, attention, and executive and psychosocial functions. The data showed persistent cognitive impairment on inhibitory control and selective attention as well as poor performance on verbal and visual memory tests in the bipolar patients. Impaired neuropsychological performance was associated with duration of illness, total number of episodes per lifetime, and previous episodes with psychotic features.

NEUROSURGERY

Interoperative use of epidural methylprednisolone or bupivacaine for postsurgical lumbar discectomy pain relief: A randomized, placebo-controlled trial

Corticosteroids and local anesthetics are widely used to decrease pain following surgery for herniated lumbar discs, but controversies still exist regarding the benefits of these drugs. Lotfinia and colleagues randomized 150 patients with single level herniated nucleus pulposus to either 40 mg methylprednisolone, 2 mL bupivacaine 5% or normal saline instilled into the epidural and exposed nerve root postoperatively following a standard hemipartial lamimectomy and discectomy. There was no significant difference in back and radicular pain intensity between the three groups, leading the authors to conclude that intraoperative administration of epidural methylprednisolone or bupivacaine does not relieve postoperative back and radicular pain.

review

Epidemiology, Clinical and Complications Profile of Diabetes in Saudi Arabia: A Review

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Diabetes mellitus is emerging as a major public health probelm in Saudi Arabia in parallel with the worldwide diabetes pandemic, which is having a particular impact upon the Middle East and the third world. This pandemic has accompanied the adoption of a modern lifestyle and the abandonment of a traditional lifestyle, with a resultant increase in rates of obesity and other chronic non-communicable diseases. The indigenous Saudi population seems to have a special genetic predisposition to develop type 2 diabetes, which is further amplified by a rise in obesity rates, a high rate of consanguinity and the presence of other variables of the insulin resistance syndrome. We highlight the epidemiology, clinical and complications profiles of diabetes in Saudi people. Diabetes is well studied in Saudi Arabia; however, there seems to be little research in the area of education and health care delivery. This is of paramount importance to offset the perceived impact on health care delivery services, to lessen chronic diabetes complications, and to reduce the expected morbidity and mortality from diabetes.

The world is witnessing a diabetes pandemic. The resource burden of the pandemic will fall primarily on developing countries.[1] It is expected that the estimated number of patients with diabetes of 150 million in the late 1990s will reach 230 million by 2010 and will rise further to 300 million by 2025.[2] Such a dramatic increase will have a significant impact on the meager health resources of the developing countries, as diabetes is a chronic disease with devastating complications, including premature atherosclerotic cardiovascular diseases, sight-threatening retinopathy, renal failure and neuropathic diseases. The Kingdom of Saudi Arabia has a relatively young population whose lifestyle has witnessed major changes in the last four decades. A significant rise in diabetes prevalence has accompanied these changes in lifestyle. In the late 1970s and early 1980s diabetes was not considered a commonly encountered medical diagnosis in Saudi Arabia even in high-risk groups,[3] and among the male Saudi population the prevalence of diabetes was not different from other parts of the world.[4] However, this seems to have changed dramatically in the last two decades, as the prevalence of diabetes in Saudi Arabia is now one of the highest in the world.[5,6]

Unique genetic and physiological characteristics of Saudis may explain in part the dramatic rise in the prevalence of diabetes. Diabetes mellitus, especially type 2 is a polygenic disorder and the high consanguinity rate among Saudis may be playing a significant role in its prevalence.[7] Furthermore, Saudi Arabs have been reported to absorb glucose more rapidly than native African people from Zambia.[8] In addition, the accompanying change in dietary habits in the last three decades, with regular consumption of large quantities of high caloric content food coupled with adoption of more sedentary lifestyle and abandonment of the traditional nomadic way of life has led to high obesity. Obesity is a well-known and strong risk factor for diabetes, especially in high-risk population.

For this review, we studied the published literature on diabetes in Saudi Arabia with the aim of getting a global picture of the condition at a time when diabetes is having an adverse effect on health care delivery. We hope the review will be a useful and comprehensive source on the subject for researchers, academics and clinicians who care for the increasing number of patients, and help health care providers curb the tide of the diabetes epidemic. We searched available articles published in Medline primarily by using the key words 'diabetes mellitus' and 'Saudi Arabia' up to the time of writing of the article. We covered the epidemiology, clinical and complications profile. We also highlight any specific features that may be rather unique to diabetes in Saudi Arabia or the Middle East.

Epidemiology of Diabetes in Saudi Arabia

Table 1 summarizes the various epidemiological studies that were published in Medline between 1982 and 2004. The first study by Bacchus et al (1982)[4] studied a small number of patients and included only male civil service subjects from a small rural area outside Riyadh in the Central region. The study showed a prevalence of 2.5% and despite its several limitations the study highlights important features. About 65% of those with diabetes were overweight, and the quoted prevalence is higher than that reported by a similar study reported from India around the same time (1.6%). The next study, a single-authored study published in 1986, involved a small group of male and female subjects.[10] It had the same flaws of involving a small number of subjects, only those from a rural area in the Western part of Saudi Arabia.[9] However, it indicated the rising rate of diabetes, quoting a prevalence of 4.3%, and showing in addition, high obesity rates among the diabetic subjects (42%) compared with controls (28%). It also showed that diabetes was more common among affluent subjects. The next study was also a single-authored study by Anukote.[11] It shares the same flaws, i.e., a relatively small number of subjects not representative of the whole population. No females were studied; it included only university staff from Riyadh (an urbanized population). Its main advantage is that it confirmed the trend of a rising diabetes prevalence (6%).

The study by el-Hazmi et al (1996)[12] was devoid of the many limitations of the previous studies. It involved a large number of subjects (23 493) and both sexes of the age group 2-70 years were included. It gave for the first time a prevalence rate of type 1 diabetes (0.21%) and of impaired glucose tolerance (IGT) (0.715%), in addition to an overall prevalence of type 2 diabetes (4.99%). Furthermore, it showed gender difference in diabetes prevalence (4.5% for females and 5.5% for males). It also pointed to the rise in prevalence of type 2 diabetes and IGT with age, reaching 17% and 12% for the former and 1.3% and 2.2% for the latter for males and females >30 years of age, respectively. In a follow-up report published in the year 2000 by the same authors,[13] the prevalence of diabetes in males was 9.7% and in females 7% in a subset group of their original cohort who were >14 years of age. The highest prevalence of diabetes was among subjects from the northern region of Saudi Arabia. They also showed that there was a parallel rise in obesity rates with a higher rate in females (20%) vs males (13%).

A report of the household survey for chronic metabolic diseases by Al-Nuaim[5] (Table 1) was able to map out age and gender differences in diabetes prevalence in both urban and rural areas. The prevalence of diabetes among females was 14% and 9% and that among males was 12% and 7%, from urban and rural areas, respectively. The prevalence of diabetes in urban male populations in the age group 15-20 years was 2%, increasing dramatically to 49% in the female age group 51-60 years. By contrast, the corresponding prevalence of diabetes in rural areas was 1% and 29% in the same groups. The study confirmed a higher prevalence of obesity among urban females. The study also showed that age, obesity and a family history of diabetes was more common in those with diabetes. The main limitation of this study (by

Table 1. Epidemiological studies of diabetes in Saudi Arabia, 1982-2004.

Study	Year	No subjects	Urban	Rural	Method	Prevalence	Comments
Bacchus et al[4]	1982	1385	No	Yes	OGTT	2.5%	Only males
Fatani[10]	1987	5222	No	Yes	RBG/OGTT	4.3%	Only males
Anokute[11]	1990	3158	Yes	No	Urine / FBG	6.0%	
el-Hazmi et al[12]	1996	23 493	Yes	Yes	OGTT	5.0%	
Al-Nuaim[5]	1997	13 177	Yes	Yes	RBG/OGTT	12.0%(M), 14.0% (F)	Urban
						7.0% (M), 9.0% (F)	Rural
el-Hazmi[13]	2000	15 493	Yes	Yes	OGTT	9.7% (M), 7.0% (F)	
Al-Nozha[6]	2004	16 817	Yes	Yes	FBG	23.7%	Cut off age > 30 y

FBG: fasting blood glucose, OGTT: oral glucose tolerance test, RBG: random blood glucose. (M): male, (F): female.

today's standard) is that it used random blood glucose as a screening method so a significant number of subjects with diabetes might have been missed. However, at the time of the study WHO recommended using the random blood glucose as the tool for use in epidemiological studies. In a further paper by the same author, the diabetic group had more abnormalities of lipoprotein profiles, which is further amplified by overweight and obesity, thus confirming a link in the various components of insulin resistance syndrome in Saudi Arabs.[14]

The latest national epidemiological survey by Al-Nozha et al (2004),[6] like the report by Al-Nuaim, has the major advantage of being representative of the whole population, in addition to using a lower cut off value for fasting blood glucose as the screening method, according to latest ADA/WHO diagnostic criteria. However, its major weakness is that it only screened subjects older than 30 years of age, so the quoted overall prevalence rate (23.7%) may have been artifactually increased. It also confirmed the effect of urbanization, with a higher rate in urban (25.5%) vs the rural areas (19.5%).

In summary, all published epidemiological studies, despite the major limitations of the earlier ones, have pointed to an exponential rise in diabetes prevalence coupled with a parallel rise in obesity rates. It is an irony that in the Al Nuaim study the areas of least economic development (the southern region) have the least prevalence of diabetes despite a higher consanguinity rate, suggesting that environmental factors are far stronger than genetic factors in the dramatic rise of diabetes prevalence. Also, several of the studies confirmed the effects of urbanization and the concomitant parallel rise in obesity rates, both of which may have played a significant role in the rise in diabetes prevalence.

Specific Diabetes Syndromes

Type 1 diabetes mellitus

The main study that examined the prevalence of type 1 diabetes at a population level was that by el-Hazmi et al (1996).[12] This study included about 8000 children younger than age 14 years and the prevalence of type 1 diabetes was reported as 0.017%, with females showing more preponderance. An earlier study involved only 110 children from a single centre in Riyadh[15] who were diagnosed and followed up between 1985-1989. This study showed a mean age of onset of diabetes of 5.9 years, with 30% of the cohort less than 3 years of age; 31% of the children were from first-degree consanguineous marriages. Another small study by Kulyate and Narchi (2000)[16] from the Eastern Province showed a significant increase in the incidence of type 1 diabetes between 1986 and 1997. The increase was mainly in girls and in those older than age 10 years. In the study by Fonseca et al (1985),[17] the prevalence of type 1 diabetes among a cohort of 200 diabetic patients attending their hospital was 3.5% based on the presence of ketonuria, low insulin and C-peptide and the continuous need for insulin therapy. However, the same group in a later study[18] involving a larger number of patients and using the criteria of a previous episode of ketoacidosis plus the use of insulin to control hyperglycemia or the onset of diabetes below age 15 years, found a prevalence of type 1 diabetes of 11.7%, which is very much in accord with the prevalence of the disease from most parts of the world.

The HLA haplotype of class II DQB1 0201/0202 -DR104 was found to be associated with type 1 diabetes in Saudi patients whereas the presence of DPB1-0401 is protective against the disease, suggesting that the haplotype DR4 confers risk of the disease in the same way it does in other population groups.[19] Immune markers for endocrine disease were assessed in a group of diabetic children and normal controls by Abdullah et al.[20] Of the Saudi diabetic children, 14.6% were positive for islet cell antibodies vs 2.2% of the normal controls. Of interest, 56% of those tested at the onset of diabetes were positive for those antibodies. In the same cohort, 8.8% were positive for antithyroid antibodies and 9.3% were positive for parietal cell antibodies, but none had anti-adrenal antibodies. The incidence of polyendocrine deficiency syndrome is not known, but in a case report, three members of the same family had Schmidt syndrome.[21]

Other types of diabetes

A unique association of diabetes in Saudi children was found with thalassemia major, a condition that is rare in Caucasians.[22] The prevalence of diabetes was high among those thalassemic children, which was related primarily to iron overload in the liver and pancreas associated with either hypo- or hyperinsulinism. A peculiar and previously undescribed syndrome of neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, congenital glaucoma and polycystic kidneys was described in two siblings (of 4) of a Saudi family.[23] The diabetes was found to be of non-autoimmune origin. Another unusual syndrome of diabetes mellitus, hypogonadism, with other abnormalities, was reported in six members of the same Saudi family.[24] The high consanguinity rate among Saudis may prove to be crucial in such syndromes.

Gestational diabetes mellitus

Nearly three decades ago diabetes complicating pregnancy or pregestational diabetes was occasionally encountered.[3] A decade later this has changed dramatically. A study that screened 210 women using the 75-g oral glucose tolerance test after 28 weeks of gestation revealed that 19.3% had gestational diabetes.[25] The overall prevalence in this study was 10.3% on follow-up OGTT. Mwambingen et al (1988)[26] reported that gestational diabetes is particularly common in grand-multiparae. Khawaja et al (1989)[27] confirmed the earlier studies and showed an overall incidence of gestational diabetes of 11%, which is primarily influenced by parity and age. In a review of prenatal care in primary care health services in the Eastern province of Saudi that included 10 594 women the prevalence of diabetes among those women, was found to be 17%.[28] Offspring of Saudi diabetic mothers have a higher rate of infant morbidity compared to those born to non-diabetic mothers,[29] and this is characterized by excess macrosomia and operative delivery.[30] On the other hand, perinatal mortality was shown to be higher in the offspring of the diabetic mothers compared to those without diabetes.[31] There was no difference in perinatal complications in those born to mothers with pregestational and those whose mothers have gestational diabetes.[32]

A report by Narchi and Kulyate showed a high prevalence of Down syndrome in infants born to Saudi mothers with gestational diabetes.[33] All affected children had trisomy 21 and there was no age difference between those who had children with Down syndrome and those who did not.

In summary, there is a parallel rise in the prevalence of gestational diabetes in common with the trend for rise in type 2 diabetes and this is associated with significant morbidity and mortality. However, other correlates for a rise in prevalence, like family history and obesity, has not been characterized by those studies. More data is needed in this area.

Maturity onset diabetes of the young

To date only few reports have pointed to the presence of this specific type of diabetes in Saudi Arabs.[12,17] El-Hazmi et al (1996) postulated that the condition was present in 13 children below age 14 years with diabetes whose diabetes did not require insulin therapy to control glycemia, and they had other members in the family who suffered from diabetes, but no scientific data or case report confirmed this.[12]

Type 2 diabetes, insulin resistance syndrome, metabolic risk factors and macrovascular disease

As in most parts of the world, diabetes in Saudi people is mainly type 2,[17,18] clustering with obesity, dyslipidemia and other variables of the insulin resistance syndrome.[5,6,12,13] Dramatic changes in lifestyle with resultant obesity and possible genetic predisposition are probably responsible for the diabetes epidemic in Saudis, which is akin to other populations who witnessed similar changes.[34] A possible interaction of high consanguinity rate to familial aggregation has been suggested.[35]

Among Saudis, glucose intolerance is a major risk factor for vascular events,[36] especially cerebrovascular disease[37] and myocardial infarction,[38] and especially in young patients.[39] In one study, diabetes was a predictor of acute myocardial infarction in patients attending primary health care centers.[40] Obesity and being overweight are major variables of the insulin resistance syndrome in Saudi Arabs and are strongly linked to type 2 diabetes. The diabetes epidemic has paralleled the upsurge of obesity in Saudis. El-Hazmi and Warsy studied the prevalence of obesity among 1419 patients with diabetes and 13 241 non-diabetic subjects from different regions of Saudi Arabia. They found that obesity (BMI >29 kg/m^2) and overweight (BMI 25-29kg/m^2) is present in 30% and 33% of those with diabetes but only in 16% and 25% of those without diabetes, respectively.[13] In the report by Al-Nuaim, (1997) diabetes and impaired glucose tolerance were increased in those who were overweight or obese,[14] with impaired glucose tolerance more common in overweight males and diabetes more common in overweight and obese females. In that study the overall prevalence of overweight and obesity in either sex exceeded 60%, which is one of the highest rates in the world.[41] In another study, only 19% of diabetic and hypertensive patients attending primary care services were within their ideal body weight, and only 9% of females had a BMI <25kg/m^2.[42]

Recently, AlHarthy and AlGhamdi, (2005) reported a significant relationship between serum resistin, a possible marker of insulin resistance, and all indices of body weight in diabetic and non-diabetic female Saudi women, implying that overweight Saudi females are at high risk of developing diabetes.[43] Furthermore, Aldaghri et al (2005) showed that serum resistin is related to both LDL and CRP, providing a possible link between insulin resistance, hyperlipidemia and inflammation.[44]

Hypertension is linked with diabetes in Saudis; however, the strength of its relationship seems to be conflicting. Akber found that hypertension was present in 60% of the 427 patients with diabetes who were admitted to hospital,[45] and this is strongly linked with other cardiovascular complications, renal failure and higher mortality. However, Warsy and el-Hazmi (1999), in their epidemiological survey, reported that hypertension was present in 5.4% of males and 3.7% of females.[46] The difference between the two studies is likely related to selection bias and the small number of patients in the earlier study. Their finding is confirmed by Al-Shammari et al (1994).[47]

In the study by Al-Nuaim (1997), lipoprotein abnormalities were common in diabetic Saudis with high numbers in the 90th centile of serum total cholesterol concentration across the various age groups, but was less severe than their age- and sex-matched European counterparts.[36] Of the study cohort, 50% had low HDL and this was associated with overweight or obesity. High triglycerides were found mainly in males with glucose intolerance and to a lesser extent in females, despite the females having higher BMI. The combination of low HDL and high TG reflects the atherogenic lipoprotein phenotype in Saudis as a refection of insulin resistance.

Among patients with stroke, 37% to 41% have diabetes[48,49] and diabetes is a major risk factor among patients admitted to the hospital with stroke disease. Diabetes also contributes to morbidity, mortality and long hospital stay.[50] Young Saudi diabetics are more prone to lacunar cerebral infarct.[51] Furthermore, diabetes was shown to be a major contributor to peripheral artery disease in Saudis with 61% of those with diabetes having peripheral artery disease.[52] On the other hand, diabetes is a well documented predictor of coronary artery thrombosis in patients in primary care,[40] despite the fact that to date no study has assessed the prevalence and severity of coronary artery disease in Saudi patients with diabetes.

The study by Al-Nozha et al (2002) assessed the level of homocysteine, the independent vascular risk factor, and found that it is lower in Saudi diabetic patients,[53] in contrast to the study by Ajabnoor et al.[54] Interestingly, Ajabnoor et al showed a linear relationship between LDL and homocysteine, an observation documented before in young menstruating Caucasian females.[55] More data is needed to resolve this disparity. C-reactive protein (CRP), a surrogate for inflammation and excess vascular risk was reported to be reduced by metformin but not by glibenclamide in a group of Saudi patients with type 2 diabetes.[56]

Diabetic retinopathy

Among Saudi patients, the prevalence of retinopathy is 31% after a mean duration of diabetes greater than 10 years.[57] This is in keeping with data from the Diabetes Control and Complications Trial involving type 1 diabetes patients from the USA as well as data from the United Kingdom involving type 2 diabetes patients.[58,59] The duration of diabetes and the incidence and severity of retinopathy are closely associated.[57] In patients with type 1 diabetes, the incidence rose from 6.1% in those with diabetes duration ≤5 years, to 62% in those who had the disease for ≥10 years. For persons with type 2 diabetes the incidence rose from 10% to 50% for those with a similar duration of diabetes. No proliferative retinopathy was seen amongst type 1 diabetes patients with disease duration ≤5 years and only in 0.8% of those with type 2 diabetes. In those with disease duration ≥10 years, 9% of those with type 1 diabetes and only 2.1% of persons with type 2 diabetes had proliferative retinopathy. Insulin use is a significant factor associated with the incidence of retinopathy and in those with type 1 diabetes who had an increased incidence and severity of retinopathy compared to persons with type 2 diabetes (43% and 6% vs. 25% and 1.5%, respectively). In addition to longer diabetes duration, poor glycemic control, hypertension and raised serum cholesterol are the main risk factors for development of retinopathy in all groups. The presence of nephropathy correlated with severity in all age groups. In another study by the same group,[60] the presence of retinopathy was a strong predictor for the presence of other diabetic complications in both type 1 and type 2 diabetes patients. Among 90 patients with retinal vein occlusion, 31% had diabetes and in nearly one third the occlusion was attributed to intense dehydration whilst fasting during the wholly month of Ramadan.[61] In summary, data on diabetic retinopathy in Saudi patients, albeit scarce, seems to be in agreement with data from other parts of the world. However, to date no study has examined screening strategies for diabetic retinopathy in Saudi patients.

Diabetic neuropathy and foot disease

Preliminary data from the Western part of Saudi Arabia suggests that the overall prevalence of neuropathy in diabetic patient is 82%, which is one of the highest in the world.[62] Among those with neuropathy, 57% were asymptomatic, implying subclinical disease, and symptomatic disease is related to old age, longer duration of diabetes, poor diabetes control, type 2 diabetes and smoking. On the other hand, a study by Fonseca et al found relatively common abnormalities in tests of autonomic nerve dysfunction in a group of patents who had a relatively short duration of diabetes, implying a longer duration of subclinical diabetes in Saudi Arabs.[63] The same group confirmed their earlier finding by documenting prolonged cardiac systolic time, a surrogate for cardiac autonomic neuropathy.[64] In a comparative study between a group of Swedish patients with diabetes and similar age- and sex-matched Saudi patients, Neilsen (1998) found that the prevalence of diabetic neuropathy was similar in both groups.[65] However, the occurrence of foot ulcers and the amputation rate was significantly lower in the Saudi group. These findings were similar to a recent report by Abbott et al (2005) on the lower prevalence neuropathy and foot complications in Asians and Afro-Caribbeans compared to Caucasian diabetic patients in the UK.[66]

Qidawi et al (2001) reported that 29% of Saudi patients with diabetic peripheral neuropathy have some features suggestive of diabetic neuroarthropathy, and that 18% of those patients underwent foot amputations.[67] In a study by Akbar and Qari (2000), which looked exclusively into diabetic foot lesions in Saudi diabetics, but involved a small number of patients, found that the problem is mainly seen in males, and that 23.5% ended with major amputations.[68]

Erectile dysfunction in patients with diabetes is primarily related to neurovascular dysfunction. In a study by El-Sakka and Tayeb, a high prevalence of erectile dysfunction is reported among their study cohort of Saudi patients with type 2 diabetes, but other confounding factors like other endocrine disease and use of various medications may have overestimated their finding.[69] Al Helali et al studied 388 patients with erectile dysfunction and found that 30% of them had diabetes.[70] Management of these patients is hampered by several economic, social and educational factors.[71]

Diabetic nephropathy

There is a global increase in the scale of diabetic chronic kidney disease with a resultant increase in those requiring renal replacement therapy, in the aftermath of the diabetes pandemic worldwide. Saudi Arabia is no exception. Despite that data on diabetic nephropathy in Saudi are scarce,[72] diabetes is responsible for 30% to 45% of those requiring dialysis.[73] Al-Zaid et al (1994) screened 211 patients with type 2 diabetes for microalbuminuria (MA) and found that 41.3% had MA and 12.8% had dipstick positive proteinuria. The subjects with MA had higher fasting blood glucose and BMI, but there was no difference in the levels of total cholesterol, the presence of hypertension or length of diabetes duration between those with and those without MA.[74] No follow-up data is available from this study, nor is there to date any data on patients with type 1 diabetes. Furthermore, MA in type 2 diabetes may represent a marker of vascular dysfunction and vascular risk rather than an exclusive indication of future development of diabetic end-stage real disease (ESRD).

In a case-notes review study, Al-Hamrany and Abdelmoniem (2004) examined 208 patients with type 2 diabetes attending primary care services in the southern region. Dipstick positive proteinuria was found in 54% of patients and this was associated with poor diabetes control and dyslipidemia.[75] However, this study had several limitations, including ascertainment bias of those with proteinuria, and methods of assessing overall glycemic control. In Caucasians with diabetic microalbuminuria, 20% to 40% develop overt nephropathy in 6 years, compared to 37% to 40% of Pima Indians with MA over a 4 to 5 year period.[76] Preliminary data from Saudi Arabia is in accord with the latter.[72]

In a study involving a small number of patients, Al Khader (2001) followed up 28 patients with type 2 diabetes and diabetic nephropathy (confirmed by renal biopsy) and found that 43% became dialysis dependent, 42% doubled their creatinine and only 15% had a stable course.[72] This confirms that the rate of progression of diabetic nephropathy in Saudi patients is alarmingly fast when compared with data reported from Pima Indians.[76] The dialysis population in Saudi Arabia has grown from only 370 patients in early 1980s to 7020 patients in the late 1990s,[77] and the number of diabetic patients entering renal replacement therapy rose from 4% in early 1980s to 14.8% in the mid 1990s[78] to 40% in the late 1990s.[79] The majority of those are type 2 diabetic patients. Furthermore, mortality among those entering dialysis has increased significantly, with the majority of deaths (60%) among those with diabetes.

There is also a parallel rise in incidence of hepatitis C infection among the dialysis population,[77] and this has a special predilection for patients with diabetes.[80] In a study by Souqqiyyeh et al (1996), involving a group of patients who underwent renal transplantation in two major transplant centers in Saudi Arabia, and who were followed up between 1985-1996, 12.1% developed post-transplant diabetes (PTD) after a mean follow-up period of 67 months vs. PTD in 10% among those who had diabetes pre-transplant.[81] This rate of PTD development is similar to the rate reported from other countries.[82] The major risk factor for PTD is increasing age, but other important risk factors like family history and HLA haplotype were not ascertained. Another weakness of the study is that the follow-up was prior to the widespread use of immunosuppressants, which have a major causative role in PTD. Despite that the rate of PTD is similar to the rate in the background population in earlier studies.[5,12] Further studies are needed as this study involved only two centers, and the current scale of PTD needs to be ascertained, especially with the recent dramatic increase in diabetes prevalence in the background population as well as the increase in those with diabetic ESRD who are increasingly receiving renal transplant.

Special Features of Diabetes in Saudi Arabia

High rate of consanguineous marriage in Saudi people
Saudi Arabia has one of the highest rates of consanguineous marriage in the world. In a study by el-Hazemi et al the rate of consanguinity is reported as high as 57.7%, with first cousin marriage being 28.4% followed by distant relative marriage at 14.6%.[7] Such a high rate of consanguinity may have a special impact on a polygenic disease like diabetes mellitus, especially type 2 diabetes. Anokute, in a retrospective study of 210 cases of diabetes in the central region of Saudi, found that familial aggregation yielded an odds ratio of 6:2, which suggests a causal association with diabetes.[82] However, the number in this analysis was small, and a larger epidemiological analysis did not include this variable for analysis. One may speculate that the high consanguinity rate has a special impact on type 2 diabetes in Saudis, but the confirmation of this will await analysis involving a large number of patients. Interestingly, the impact of consanguinity is well known on inherited monogenic diseases like thalassemia and glucose-6-phosphate dehydrogenase deficiency (G6PD), and those conditions amplify diabetes in affected subjects (see below).

Hemoglobinopathies and diabetes
Patients with hemoglobinopathies such as sickle cell disease and thalassaemia may be especially prone to develop secondary diabetes following repeated blood transfusion with subsequent hemosiderosis and liver and pancreatic damage. Hemoglobinopathies are common in the Saudi population, especially in those in the Eastern province[83] where the prevalence of diabetes has been reported to be the highest in the Kingdom.[5] Diabetes among children with thalassemia is higher than in their Caucasian counterpart.[22] No study has assessed the prevalence of diabetes among children with sickle cell syndrome who are also prone to develop secondary diabetes. On the other hand, Niazi (1991) has demonstrated a high prevalence of G6PD deficiency among Saudi diabetic patients–12.4% vs. 2% in healthy non-diabetic control subjects.[84] The clinical significance of this association is not clear.

Ramadan fasting and diabetes
Saudi Arabia is an exclusively Muslim country, and fasting during Ramadan has a special impact on diabetes.[85] There is a growing body of literature on the relationship between fasting during the Holy month of Ramadan and diabetes, with fasting reported to be beneficial in patients with type 2 diabetes,[86] but potentially harmful in elderly patients, and those who are ketosis prone, and in those who have advanced complications.[87,88] Only one paper has examined the impact of Ramadan fasting on Saudi type 2 diabetic patients,[89] with no reported change in the level of fasting glucose, glycated hemoglobin, insulin, C-peptide or body weight, and with a significant rise in total cholesterol, but not triglycerides, at the end of fasting. It is an irony that the perceived benefit from fasting will require specific education and advice to patients and such education seems to be very much deficient or none existent.[90] Dehydration during Ramadan fasting may be a trigger for retinal vein occlusion in patients with diabetes.[61] Therefore, the need for more research in this area is needed,[88] especially for other rituals during Ramadan, like Umra, which may have special impact on diabetes and its complications (Elhadd et al, unpublished observations).

The Muslim Pilgrimage (Hajj) and diabetes
Every year there is a massive gathering of several million Muslims in the Holy places of Mecca and Medina. Among such pilgrims are many diabetic patients, and in general the provision of medical care to such patients is a challenging exercise. AlGhamdi et al (2003)[91] have shown that diabetes is a major co-morbid condition among those pilgrims, and that admission with medical emergencies is modified by the season of the ritual (Hajj follows a lunar calendar and it changes by approximately 11 to 12 days every year). We have recently observed that Hajj has an impact on patients with diabetes because significant numbers present to emergency medical care centers with infected foot ulcers, hyperglycemia and infections (Elhadd et al, unpublished observations).

Infections and diabetes
Patients with diabetes, in general, are more susceptible to various types of infection. Saudi diabetic patients are more prone to infection with *Mycobacterium tuberculosis*, and to viral hepatitis infections. Saudi patients with diabetes and ESRD on hemodialysis are more likely to contract hepatitis C infection than those without diabetes.[92] Conversely, patients with hepatitis C infection have a special predilection to develop diabetes. The interplay of various factors, including the genetic susceptibility, may amplify such risk further. Akbar et al (2002) have shown that Saudi patients with hepatitis C infection who develop diabetes are more likely to have a higher BMI and a positive family history of diabetes.[93] As patients with hepatitis A infection do not develop chronic hepatic sequelae, Makeen (1992) reported acute development of diabetes in three Saudi subjects with hepatitis A infection, with clinical and biochemical evidence of acute insulin deficiency (arguably resulting from pancreatic

involvement and possibly acute islitis) culminating in diabetic ketoacidosis.[94] Despite no follow-up data from this case series, a similar report from Nigeria showed diabetes to remit in six patients following acute hepatitis A infection, which recurred later in four patients.[95]

Mycobacterium tuberculosis, both pulmonary and extra-pulmonary, is on the rise in Saudi Arabia, and diabetes is a major risk factor for developing pulmonary,[96] as well as disseminated tuberculosis.[97] Nearly half of dialysis patients who had tuberculosis suffer from diabetes.[98]

Herbal medicine use by Saudi diabetics

Use of herbal medicines to treat various diseases is well-recognized practice in both developing and developed countries. In Saudi Arabia, however, the use of herbal medicine by diabetic patients seems to be high. In one study, 17% of a cohort of 296 patients from several diabetic clinics reported using herbal medicines without informing their physicians.[99] In another study by Al-Saeedi et al (2003) one-third of a cohort of 1039 patients with diabetes were using herbal medicine, and 25% of them believed that it is both safe and effective.[100] In this study, such a belief correlated with female sex, a family history of diabetes and poor compliance with diet. A study by Bugusz et al showed that herbal medicines may contain toxic materials.[101]

Conclusion

Data accumulating over the last three decades have confirmed that there is an epidemic of type 2 diabetes in Saudi Arabia. There is evidence to suggest that this has resulted from significant socioeconomic transformation with significant changes in lifestyle, mainly adoption of a Western lifestyle and abandonment of the more active tribal and nomadic-type of life. The concomitant upsurge of the epidemic of obesity is another irony of these changes. Diabetes in Saudi Arabia is well researched, especially in its epidemiology and clinical aspects. However, with few exceptions, the profile of diabetic complications needs to be better characterized. The rate of development and progression of diabetic nephropathy appears to be comparatively fast, so contributory factors needs to be explored. Also despite the high level of evidence for more severe atherosclerotic disease especially affecting young patients, more studies are needed, particularly in patients with diabetic coronary artery disease. Further, the genetics of diabetes needs to be studied, as significant genetic susceptibility is probably a major player in the diabetes pandemic. The high consanguinity rate may help to give new insights into the genetics of type 2 diabetes in general. In this regard, the possibility of new subtypes of maturity-onset diabetes of youth may be unraveled. Finally, there is a need for studies looking into models of organization of care, screening for early complications and patient education and empowerment. Measures to curb the rising rates of obesity need also to be rigorous.

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original article

Cancer incidence among the Bahraini population: a five-year (1998-2002) experience

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BACKGROUND: Cancer is the second leading cause of death, following cardiovascular diseases, accounting for 12% of annually reported deaths in Bahrain. We determined the epidemiological patterns of malignancies in Bahrain and compared them with those of other Gulf Cooperation Council (GCC) countries and other developed countries.

SUBJECTS AND METHODS: Data for the study were obtained from the Bahrain Cancer Registry (BCR) database. The overall and type-specific 5-year average incidence rates were calculated for the years 1998-2002 and derived using the CANREG software formula. The incidence rates for the year 2000 were used for comparing Bahrain with those of other countries in the Arabian Gulf using the statistics of the Gulf Centre for Cancer Registration.

RESULTS: During the 5-year period there were 2405 cancer cases in Bahrain (1239 males and 1166 females), with an annual average of 481 cases. The world age-standardized incidence rates (ASR) were 162.3 and 145.2 per 100 000 for Bahraini males and females, respectively. Generally, Bahraini men had a higher ASR for most cancer types, and the most common type of cancer was lung for males (35.2 per 100 000), followed by bladder (14.5) and prostate (14.3), and breast for females (46.8), followed by lung (12.2) and ovary (7.7).

CONCLUSION: Compared to other Gulf countries, Bahrain had higher incidence rates for cancers of the lung, prostate, colorectum, bladder, kidney, pancreas and leukemia among males and for cancers of the breast, lung, bladder, thyroid, uterus and ovary among females. A rising trend in cancer incidence is likely to continue for years or even decades to come.

Cancer is one of the major health problems in the Kingdom of Bahrain. It is the second leading cause of death, after cardiovascular diseases, accounting for 12% of annually reported deaths.[1] It inflicts a substantial burden on healthcare services, consuming a large proportion of financial and other resources.[1]

The role of cancer registries in cancer control is not equivocal.[2] Recognizing this important role, the Ministry of Health (MOH) put cancer control among its highest priorities and established a cancer registry. The establishment of the Bahrain Cancer Registry (BCR) through a ministerial decree (No. 5, 1994) was a key step in declaring cancer as a notifiable disease and laying the foundation for a database. This paper presents the first 5 years experience of the newly established registry. It describes the epidemiological patterns of malignancies in Bahrain and compares them with those of other Gulf Cooperation Council (GCC) countries and other developed countries.

The Kingdom of Bahrain is located centrally on the southern shores of the Arabian Gulf, and comprises of an archipelago of islands with a total land area of 717.5 square kilometers. Bahrain island is the largest of these islands accounting for nearly 83% of the total area of the Kingdom including the capital, Manama.[3] According to the 2001 census, the total population of Bahrain was 650 604 persons of whom 405 667 (62.4%) were Bahraini and 244 937 non-Bahraini. The growth rate between the 1991 and the 2001 censuses was 2.7% for the total population, 2.5% for the Bahraini and 3.1% for the non-Bahraini.[4] The 5-year average estimated mid-year population for 1998-2002 was 638 033 of whom, 398 455 (62.5%) were Bahraini, and 239 578 (37.5%) were non-Bahraini.[3] It should be noted here that the majority of the non-Bahraini population (69.2%) are males, who form the major part of the working force. The non-Bahraini population is unstable, characterized by a very rapid turn over during the year, and their transitional nature could affect the interpretation of cancer occurrences.

The government is committed to providing a high standard of comprehensive health care to residents,[5] including public health, and primary, secondary and tertiary care services. Primary health care is delivered through a network of 22 well-equipped health centers, staffed with qualified family physicians and allied health personnel and distributed in all geographic regions. General and specialized secondary care is provided through the main government hospital, Salmaniya Medical Complex (SMC), which has recently been expanded to house the new Oncology Services Centre that is equipped with the latest diagnostic and therapeutic technology to provide different types of treatment including chemotherapy, radiotherapy, immunotherapy and bone marrow transplantation.[1] The Bahrain Defense Force (BDF) Hospital is the second general secondary hospital that primarily serves Ministry of Defense employees and their families and accommodates the centre for cardiac surgery in the country. Secondary care is also provided by six other private hospitals. Together, the government and private hospitals have a capacity of around 2000 beds and ratios of 22 doctors of different specialties and 50 nurses for every 10 000 population.[1]

SUBJECTS AND METHODS

The BCR is a population-based registry where all physicians in the Kingdom were requested in 1994, following the ministerial decree, to report all cancer cases to the Cancer Registry Office, which is organizationally annexed to the Medical Review Office at SMC. A full-time epidemiologist and a part-time medical records technician working as a tumor registrar operate the registry.

Cases included in the study were those registered as having a malignant disease in the BCR between 1 January 1998 and 31 December 2002, whether the cancer was microscopically or clinically diagnosed. Personal, clinical and tumor details are entered in the registry using a specially designed registration form, and checked for duplication and consistency using the CANREG IV software that was developed by The International Agency for Research on Cancer (IARC) specifically for cancer registration.[6] Coding anatomical sites and morphology of tumors is done according to the International Classification of Diseases for Oncology (ICD-O-3).[7]

In addition to passive notification, case finding is enhanced by several approaches. First, medical records of patients admitted with cancer to SMC, which is the main source of cases, are sorted at the Medical Record Department upon discharge and checked for their registration status. Second, the Registrar visits the BDF Hospital periodically to review and identify lists of newly diagnosed cases. Third, the Registrar also receives cancer death notifications from the Birth and Death Registration Office, MOH, on a regular basis. The "Death Certificate Notification" (DCN) cases are cross-matched with the registered cases to sort out the unmatched cases (true DCN), which are then followed back for any hospital information related to malignancy and date of diagnosis. Of these true DCN cases, any case would be registered as an ordinary one if there were enough information indicating that it was an incident case. Those with insufficient clinical data or if the information was not indicative of the cancer are registered as "Death Certificate Only" (DCO) cases.

Using the check program, which is built-in within the CANREG software, data were examined for duplicate registration as well as for illogical errors in combinations of variables such as site-sex, site-morphology and age-morphology. Data was also checked for illogical combinations that could not be captured by CANREG such as morphology versus basis of diagnosis (e.g., leukemia), behavior versus stage codes (for in-situ), basis of diagnosis versus status codes (for DCO) and morphology versus stage. Cases in which diagnosis was based on the histology of metastasis (secondary site) were reviewed to ensure that the depicted site was for the suggested primary and not for the secondary tumor. Missing date of birth was replaced by the first two digits of the Central Population Register number, which represents the year of birth. In this case, the first of January was designated to complete the full date of birth. Missing data for unknown primary site and other variables were sought and recorded when found.

Incidence rates were calculated from the CANREG software, in which crude total and age-sex-specific incidence rates (ASPRs) for each type of cancer were calculated by dividing the number of registered cases in a year by the corresponding estimated mid-year population for the same year, the latter being an approximation of the person-years at risk.

The 5-year average total and ASPRs for the period from 1998 to 2002 were calculated according to the method used in "Cancer Incidence in Five Continents".[8] In this method, the total number of cases registered in the 5-year period is divided by person years at risk derived by multiplying the mid-year estimated population of the middle year (2000) times the number of years of the study period (five years). Rates were standardized for age and sex, by the direct standardization method using the world standard population supplied by the CANREG software.

The age-standardized incidence rates (ASRs) of some of the leading cancers in Bahrain in the year 2000 were compared with the corresponding rates for the same year for Kuwait, Oman and Saudi Arabia.[9] These countries were chosen because they have good national coverage and reliable cancer registries, and as data for the 5-year period is not available for these countries, the year 2000 was taken to represent the mid-year of the 1998-2002 period.

RESULTS

Overall cancers

During the 5-year period (1998-2002) there were 2405 cancer cases in Bahrain (1239 males and 1166 females) with an annual average of 481 cases. Of the males, 962 were Bahraini and 277 non-Bahraini. The corresponding figures for females were 964 and 202, respectively. The average annual crude incidence cancer rates for males were 95.7/100 000 among the Bahrainis, 33.4/100 000 among the non-Bahrainis, and 67.6/100 000 among all males combined. The corresponding rates for females were 97.7, 54.7 and 86.0 per 100 000 women, respectively. The world ASRs were 162.3 and 145.2 per 100 000 among Bahraini males and Bahraini females, respectively. The corresponding rates for the non-Bahraini males and females were 116.3 and 115.4 per 100 000, respectively, and the ASR for both Bahrainis and the non-Bahrainis were 147.7 and 139.1 per 100 000, respectively. Generally, ASPRs increased with age for both Bahraini and non-Bahraini males and females (Figure 1). Compared to males, females showed higher rates at young ages and lower rates at older ages among both Bahrainis and non-Bahrainis.

Cancer among the Bahraini population

Bahraini males had higher ASRs than females in almost all common cancers except thyroid cancer (Table 1). Bladder cancer was four times more common, cancer of the lung almost three times more common while colorectal and pancreatic cancers were two times more common among males than females. In contrast, thyroid cancer was almost seven times more common among females than males.

Bronchial and lung cancer is the commonest cancer among Bahraini males, followed by bladder, prostate, colorectal cancers, and leukemia (Figure 2). The commonest five cancers among Bahraini females are breast, lung, thyroid, ovary and colorectal (Figure 3).

The ASPRs of the five commonest cancers among Bahraini males and females (Figures 4, 5) indicate large gaps between the leading cancer in each sex and other cancers at all age groups. Lung cancer among males increases steeply with age, particularly at the older ages. Breast cancer has a bimodal distribution among Bahraini females with the first mode between the mid 40's and the mid 50's and the second at the 65-69 years age group. Prostate cancer has a pattern similar to that of lung cancer among males but with a delayed start.

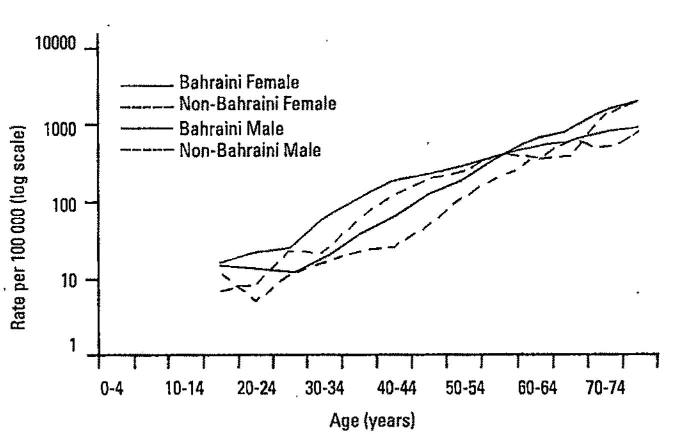

Figure 1. Average age-specific incidence rates of all cancers by nationality and gender, 1998-2002

Table 1. Age-standardized rate (world)/100 000 for common cancers among Bahraini males and females, 1998-2002.

Cancer type	Male	Female	M/F
Trachea, bronchus and lung (C33-34)	35.2	12.2	2.9:1
Colorectal (C18-20)	12.8	7.3	1.8:1
Leukemia (C91-95)	9.1	4.4	2.1:1
Bladder (C67)	14.5	3.8	4.4:1
Non-Hogdkin's lymphoma (C82-85;96)	7.9	5.8	1.4:1
Stomach (C16)	8.7	5.4	1.6:1
Thyroid (C73)	1.1	7.6	1:6.9
Kidney (C64-66;C68)	5.2	3.5	1.4:1
Liver (C22)	5.2	3.5	1.5:1
Pancreas (C25)	4.9	2.8	1.8:1

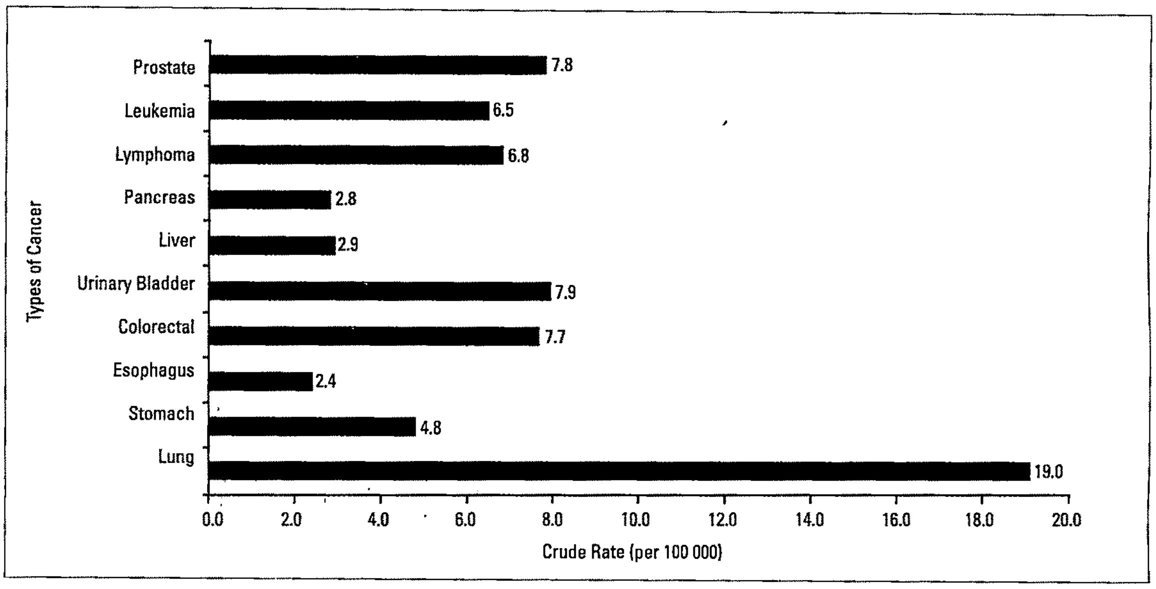

Figure 2. Incidence rates of commonest types of cancer among Bahraini males, 1998-2002.

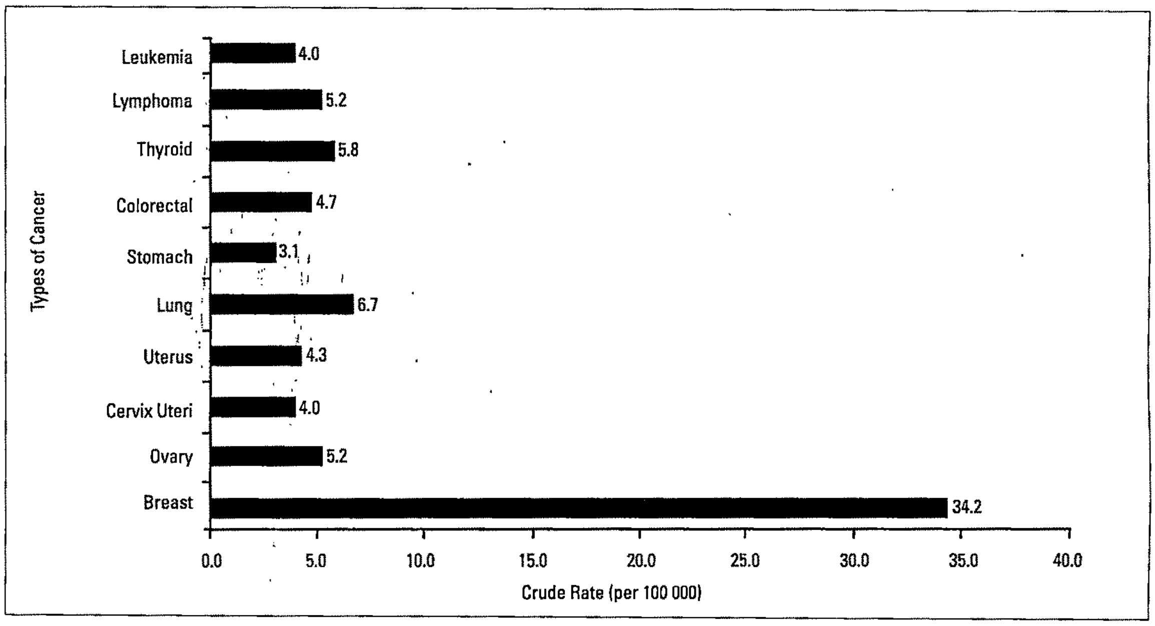

Figure 3. Incidence rates of commonest types of cancer among Bahraini females, 1998-2002.

Bladder cancer directly increases with age after the age of 40 years among males. In males, leukemia has a similar pattern as that of prostate cancer but with lower rates at all age groups. Colorectal cancer in males has a peak in the 70-74 years age group. Lung cancer among Bahraini females has an identical age pattern as that of the males with lower rates at all age groups. Colorectal cancer among females has a slow and gradual increase with a peak at the age 55-59 years and higher rates from 65 years and above. The ASPRs of colorectal cancers among females are lower than their male counterparts. Ovarian cancer has a bimodal distribution with age while thyroid cancer is unimodal with its highest peak at the age of 60-64 years.

Comparing of the sex-specific cancers among the Bahraini with their counterparts in GCC countries population, Bahraini females have the highest incidence rates of breast, uterus and ovarian cancers and the sec-

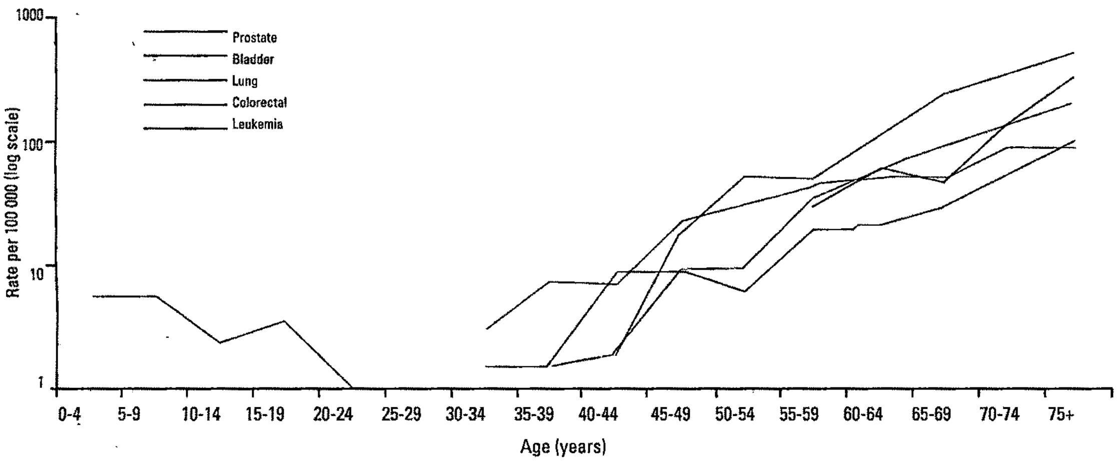

Figure 4. Age-specific incidence rates of five commonest cancers among Bahraini males, 1998-2002.

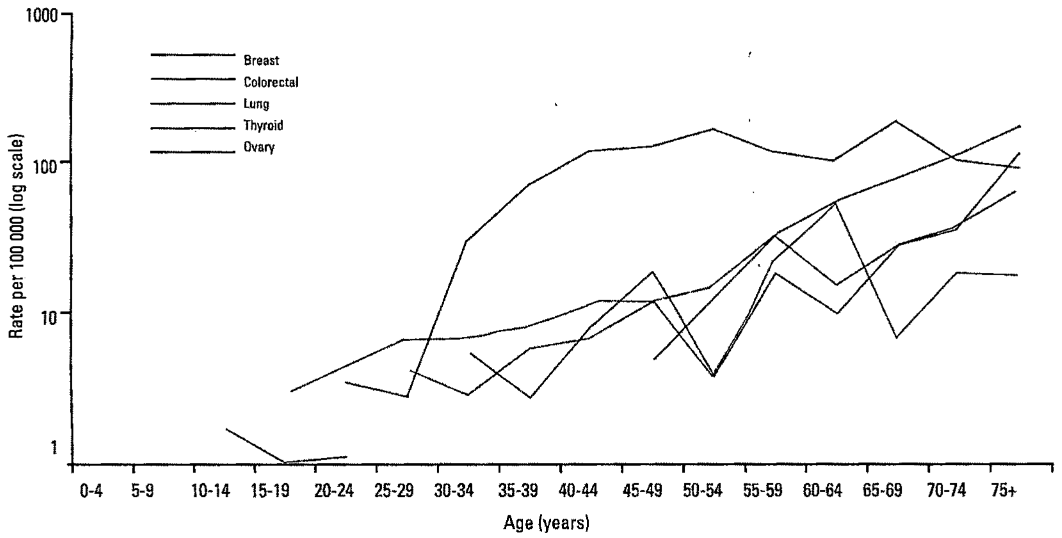

Figure 5. Age-specific incidence rates of five commonest cancers among Bahraini females, 1998-2002.

ond for cervical cancer among GCC countries, and Bahraini males have the highest ASR for prostate cancer in the year 2000 (Tables 2, 3). The ASR for breast cancer among Bahraini females in that year was 57.2 per 100 000. The corresponding rates for Kuwaiti, Omani and Saudi females were 41.7, 14.9 and 13.9 per 100 000, respectively. The ASRs for ovarian and endometrial cancers among Bahraini females were 8.2 and 5.5 per 100 000, respectively. The corresponding rates were 4.3, and 3.0 for Kuwaiti, and 6.0, 1.3 for Omani, and 2.2 and 2.4 per 100 000 for Saudi females, respectively. Bahrain ranks second to Oman in cancer of the cervix, the rate being 4.4 per 100 000 in 2000 for the Bahraini and 7.0 per 100 000 for the Omani females. The rates for Kuwaiti and Saudi females in 2000 were 2.3 and 2.1 per 100 000, respectively (Table 2). The ASR for cancer of the prostate among Bahraini males was 19.3 per 100 000 in 2000. The corresponding rates in the same year were 7.3, 8.7 and 3.6 per 100 000 among Kuwaiti, Omani and Saudi males (Table 3).

Table 2. Age-standardized rate (world)/100 000 for common cancers among Bahraini females and their counterparts in selected Gulf Cooperation Council countries, 2000.

Site (ICD-10)	Bahrain	Kuwait	Oman	Saudi
Breast (C50)	57.2	41.7	14.9	13.9
Trachea, bronchus and lung (C33-34)	12.3	2.7	2.0	1.3
Colorectal (C18-20)	9.0	14.7	4.4	4.5
Cervix uteri (C53)	4.4	2.3	7.0	2.1
Uterus (C54-55)	5.5	3	1.3	2.4
Ovary (C56)	8.2	4.3	6.0	2.2
Leukemia (C91-95)	2.6	2.5	4.1	3.1
Bladder (C67)	3.7	1.8	1.5	1.0
Non-Hogdkin's lymphoma (C82-85;C96)	5.1	3.5	5.4	3.9
Stomach (C16)	6.5	0.9	5.6	1.5
Thyroid (C73)	8.1	5.0	4.0	4.5
Kidney (C64-66;C68)	5.6	0.8	1.9	0.9
Liver (C22)	7.3	0.6	3.1	2.7
Pancreas (C25)	2.1	1.5	1.2	0.8

Table 3. Age-standardized rate (world)/100 000 for common cancers among Bahraini males and their counterparts in selected GCC Countries, 2000.

Site (ICD-10)	Bahrain	Kuwait	Oman	Saudi
Trachea, bronchus and lung (C33-34)	33.5	16.0	8.8	4.3
Prostate (C61)	19.3	7.3	8.7	3.6
Colorectal (C18-20)	12.5	10.2	4.1	4.7
Leukemia (C91-95)	7.1	2.8	5.9	3.4
Bladder (C67)	14.5	6.0	3.6	3.7
Non-Hogdkin's lymphoma (C82-85;C96)	5.6	10.1	7.7	5.3
Stomach (C16)	11.2	2.5	13.2	2.7
Thyroid (C73)	1.6	1.5	1.1	1.4
Kidney (C64-66;C68)	6.5	5.9	2.6	1.9
Liver (C22)	7.4	4.0	5.9	6.1
Pancreas (C25)	4.1	2.3	2.3	1.5

Cancer of the lung was highest in the Bahraini compared to their Kuwaiti, Omani and Saudi counterparts in that year. It was 8 times more common in Bahraini than Saudi males and nearly 10 times more common among the Bahraini than the Saudi females. Bahrain had the highest rates of bladder cancer in both sexes compared to the other GCC countries. The male rates were 3.9 times higher in the Bahraini compared to the Saudi, 4 times compared to the Omani and 2.4 times compared to the Kuwaiti. The Bahraini female rates were 3.7 times that of the Saudi, 2.5 times that of the Omani and 2 times of the Kuwaiti female rates for bladder cancer. Bahraini females had the highest incidence rate of thyroid cancer in the GCC countries while the Bahraini males had a very slightly higher ASR. Bahraini males had also the highest rates of colorectal, kidney, liver and pancreatic cancers. Moreover, the Bahraini females had the highest ASRs in GCC countries for cancers of the stomach, kidney, liver and pancreas. Bahraini males were second for stomach cancer while females occupied the same rank for colorectal cancer and leukemia (Tables 2, 3).

DISCUSSION

Before any interpretation of the findings can be made, completeness of registration and the quality of the data need to be addressed. It is known that in their early stages registries face a problem of incompleteness, which improves when more vigilant quality control measures are applied and the awareness of notifying physicians of the existence and benefits of the registry increases.[10] Cancer registration in Bahrain started in 1994 and, as with any newly established registry, there were some difficulties in ascertaining all cases and gathering all the required information as well as in coding and validation procedures. From 1998 onward, registration was done following a set of rules described in the manual of registration of the World Health Organization[11] and checking the data through CANREG software. As for the coverage, in the years prior to 1998, registered cases were those reported from the SMC, the only hospital that provided oncology care and radio- and chemotherapy in the country. Coverage is considered good as not less than three fourths of the cases in Bahrain are diagnosed at SMC. The cooperation with the BDF Hospital, since 1998, yielded better coverage, especially for cases that might be diagnosed and treated overseas. Moreover, coverage is further enhanced by the routine cross-checking of the BCR with the death register.

Taking into consideration possible artifacts in the currently presented incidence statistics of the disease, Bahrain is right in the heart of the third stage of transition, according to Omran's theory of epidemiologic transition,[12] where chronic diseases, namely those of the cardiovascular system, cancer and diabetes are dominating the main burden of disease. They account for more than half of reported annual deaths, with cancer occupying the second rank of leading causes of death following cardiovascular diseases.[1] This is in line with lifestyle changes that have taken place in the Bahraini community in the last two decades. The prevalence of tobacco smoking is 25% in men and nearly 10% in women.[13] In fact, the phenomenon of women smoking is increasing with the spread of sheesha (water pipe) smoking, and the increase in social acceptability of this type of smoking in the Kingdom.[13] Moreover, obesity is on the increase with more than half of women and men either overweight or obese, and very few exercise regularly.[14,15]

The pattern of cancer incidence reported here for males is slightly different from that in the developed countries as lung cancer is the leading type among Bahraini men while prostate cancer has now taken the lead in many of developed countries.[16] This could partly be due to the increased screening and early diagnosis, which intensified in the western world. For females, however, the patterns are similar with breast cancer by far the leading type. Breast cancer among Bahraini women (46.8/100 000) is four times that of lung cancer (12.2/100 000), the second commonest. One distinct observation in the incidence of breast cancer in Bahraini females compared to western countries, is that it begins to increase in incidence early in a young age group, a phenomenon which could warrant some genetic predisposition that needs further study. The pattern of cancer in Bahraini males is different from that of other GCC countries. Lung cancer ranks first for Bahraini males in contrast to stomach cancer among the Omani, and leukemia among Saudi males. Breast cancer however, is the most frequent cancer in all females in the GCC countries.[9]

With the evolving lifestyle behaviors that lead to an increasing risk of cancer occurrence, along with currently modest prevention and control activities, the pattern of common types of cancer in Bahrain is likely to pursue a rising trend for years or even decades to come. This situation is challenging to the health authorities in their attempts to ameliorate the cancer burden on the community. Moreover, in the current healthcare system the government ensures availability and accessibility of cancer preventive and curative services to all residents of the country, which imposes a huge financial burden on the MOH. However, the government has a great opportunity to cut the cost by strengthening cancer preventive programs since about sixty percent of the common cancers in Bahrain are associated with smoking and diet and thus are preventable.[17] It is universally accepted that a more than 50% reduction in cancer mortality could be expected from effective anti-tobacco programs (35%) and modification of dietary habits (20%) in developing countries.[2,18] Furthermore, about a 20% reduction in breast cancer mortality is achievable through a properly designed and implemented screening program.[2,19] A recent systematic review of seven completed and eligible trials showed a similar overall reduction rate, but as the effect was lower in the highest quality trials, the authors concluded that a more reasonable estimate is a 15% relative risk reduction. Meanwhile, the authors warned of the possible harms of over-diagnosis and over-treatment that screening might cause.[20]

These promising results in all such preventive modalities are, however, not easy to achieve without the realization of the need for resources including organizational, physical and human; and the sustainable commitment to procure them. We must also understand that it is difficult to convince people to put their knowledge about healthy behaviors into practice. For example, anti-tobacco measures may take up to thirty years before their maximum impact on cancer incidence is realized. For that, scientists believe that there will be a strong role for early detection and screening, treatment and palliative care modalities for years to come. They warn that screening is not just testing. It requires goodcompliance, a high-quality test, efficient referral, effective treatment and adequate follow up.[19,21] Above all, the health authorities in Bahrain must invest heavily now in preventive cancer health care and not expect the payback until ten to twenty years from now.

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original article

Prevalence of airborne allergenic *Amaranthus viridis* pollen in seven different regions of Saudi Arabia

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BACKGROUND: *Amaranthus* pollen grains are known to be highly allergenic and a potential cause of respiratory allergic diseases. Nevertheless, data on the prevalence of *Amaranthus* pollen in the environment is limited and almost non-existent for Saudi Arabia.

METHODS: We conducted an investigation to record the airborne incidence of *A. viridis* and other allergenic pollen in Al-Khobar, Dammam, Hail, Jeddah, Jizan, Qassim and Taif, using Burkard Volumetric Samplers. The samplers were operated continuously for one year at each location.

RESULTS: The data revealed *A. viridis* as one of the major components of outdoor airspora, constituting a maximum of 96% of total pollen counts in Hail, followed by Al-Khobar (89%), Jeddah (87%), Qassim (85%), Taif (84%), Dammam (83%) and Jizan (61%). These higher percentages contributed largely to the total weed pollen catch during August to November in all seven regions. In addition, the data also showed that *A. viridis* pollen were present throughout the year with distinct seasonal variations. The diel periodicities for at least five sites averaged over a year showed mid-day to early evening maxima. The maximum concentration approached 3000/m^3 of air in October and 1827/m^3 of air in September. The data also exhibited a seasonal pattern in their maximum appearance.

CONCLUSION: Further studies related to biochemical and allergological aspects are needed to confirm the allergenic impact of *Amaranthus* pollen and sensitization in allergic individuals in the Kingdom of Saudi Arabia.

Amaranthus viridis, also called slender amaranth or pigweed, is a cosmopolitan naturally growing weed found widespread in temperate and tropical regions of the world. It grows mainly on wastelands, along water coarses and as a weed in cultivated crops. It is known to flower all through the year and produce enormous amounts of pollen in the airspora. Of several species of *Amaranthus*, only eight species are known to exist in Saudi Arabia. Among these, *A. spinosus*, *A. graecizans*, *A. viridis* and *A. lividus* are considered the most common weeds.[1]

Allergenicity to a few species of *Amaranthus* pollen has been reported.[2,3] Many genera belonging to Chenopodiaceae and Amaranthaceae are also well known for causing pollinosis.[2,4] However, only a few reports have documented the airborne occurrence of *A. viridis* pollen.[5-9] Apparently, no detailed study on seasonal and diel periodicities of *A. viridis* pollen has been previously undertaken or published. The objective of the current study was to determine the airborne incidence of *A. viridis* pollen in different regions in Saudi Arabia, and to describe their seasonal and diurnal (diel) periodicities.

METHODS

Atmospheric samplings at seven major regions (Al-Khobar, Dammam, Hail, Jeddah, Jizan, Qassim and Taif) in Saudi Arabia were conducted using Burkard Seven-Day Volumetric Spore Traps. The traps were operated continuously for more than 12-month periods and one-year data were included for each site during 1994-2001.

Al-Khobar (sampled during the years 1998-1999) is a comparatively newly developed city, with major oil fields located in the region and it has become the commercial hub of the eastern province. Dammam (1999-

2000) is a newly developed business city on the east coast. Hail (1996-1997), a newly developed city in the Northern province of Saudi Arabia, is a rich agricultural region. Jeddah (2000-2001) is an ancient coastal city by the Red Sea. Jizan (1994-1995) is another ancient coastal city by the Red Sea in the Southern province. Qassim (1997-1998), located in the central province of Saudi Arabia, is mostly an agricultural region. Taif (1995-1996), located in the western province of Saudi Arabia and situated on a plateau, is a hilly summer resort with deciduous plants and highlands.

The Burkard Volumetric (7-day recording) Samplers were installed on the roof of hospital buildings and the intake orifice of the samplers was approximately 10 meters above the ground level. Samplers were set for 7-day sampling onto Melinex tape. Air was drawn through the 2×14-mm orifice at 10 L/min to impact onto adhesive-coated, transparent tape. The tapes were changed weekly and cut into one-day (24 hour) segments, which were mounted with a gelvatol-phenol mixture onto a microscopic slide. Identification and counting were undertaken in 10 random fields for each hourly count (4-mm traverse) for each 24-hour period (=240 fields). Slides were scanned at a magnification of ×400 for counting and, where necessary, ×1000 under oil immersion for identification. The trap operates on the principle of "impaction through suction" with a 2-mm movement of the drum each hour. Spores were converted to cubic meter of air by a factor obtained by applying the formula: concentration of propagules $m^3 = NT\ AE/n \times a \times V_a$, where NT is the total number of spores counted in "n" areas, n is the number of fields counted (=10 field areas), a is a field area, mm^2 (= 0.15205 mm^2); V_a is the air volume sampled $(m^3)(0.63)$ and AE is the total effective area, mm^2 (i.e. long axis of orifice × distance tape moves in hour, $14 \times 2 = 28\ mm^2$) (Hasnain et al., 1984, 2004a).[10] Based on the above equation, each hour counts were added to calculate daily mean/m^3 and monthly mean/m^3 of air.

RESULTS

The results were recorded in various individual categories. The weeds pollen group mostly included common airborne pollen grains from weeds, viz., *Amaranthus viridis, Plantago spp., Rumex vesicarius, Atriplex spp., Cyperus rotundus, Chenopodium album* and *Ricinus communis*. However, in this communication only data relating to *A. viridis* are presented. The percent catch (Table 1) of *A. viridis* pollen out of total pollen encountered from seven different regions for 12 months of the year reveals that *A. viridis* pollen constituted a maximum of 89% (October) in Al-Khobar, followed by 83% in Dammam (September), 96% in Hail (September), 87% in Jeddah (October), 61% in Jizan (October), 85% in Qassim (September and October) and 84% in Taif (October). In other months, *A. viridis* pollen were found to be less frequent in all regions. The data exhibited a distinct rise in percent catch of *A. viridis* pollen during August to November.

Data for diel periodicities are based on accumulated monthly mean values per cubic meter for each site for a complete 12 months. The data exhibit a mild trend of diurnal pattern with day time maxima for three sites (Qassim, Taif and Al-Khobar), and a clear dirunal pattern for one site (Hail) (Figure 1). At the other two sites, because of low concentration, no such trend was obtained.

The maximum concentrations of *A. viridis* pollen at the seven different sites are presented in Figure 2. The data also exhibited a seasonal pattern in their maximum appearance starting from August to November showing a peak in September and October. The maximum concentration of *A. viridis* pollen during these months reached 1827-3000/m^3 in the Hail region followed by

Table 1. Percentages of *A. viridis* pollen of total airborne pollen over sampling year for each site.

Sites	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Al-Khobar	48	31	11	17	50	48	60	68	76	89	65	49
Dammam	44	42	10	18	24	18	20	36	83	78	51	43
Hail	18	7	3	1	2	3	5	48	96	52	78	62
Jeddah	15	24	14	10	47	55	50	84	20	87	75	68
Jizan	3	3	0	0.4	0.3	2	0	26	61	56	7	0
Qassim	31	38	28	21	45	41	31	56	85	85	80	67
Taif	1	2	2	0.5	0.1	0.4	3	9	80	84	25	6

Numbers are percentage. 0=no pollen.

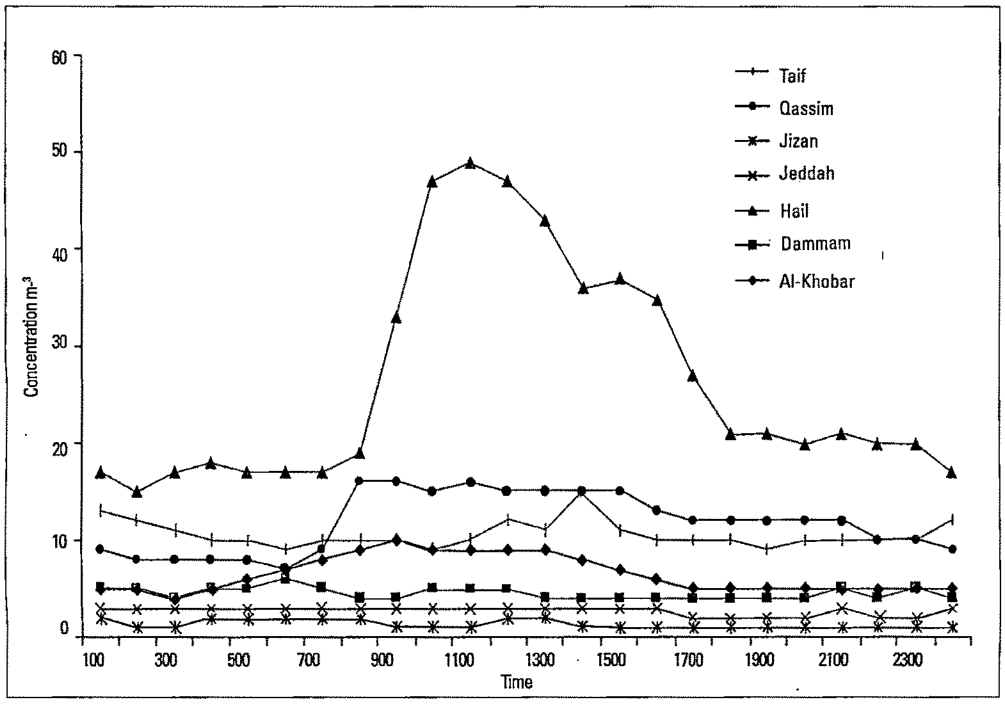

Figure 1. Diel periodicities of airborne *Amaranthus viridis* pollen in seven different regions of Saudi Arabia.

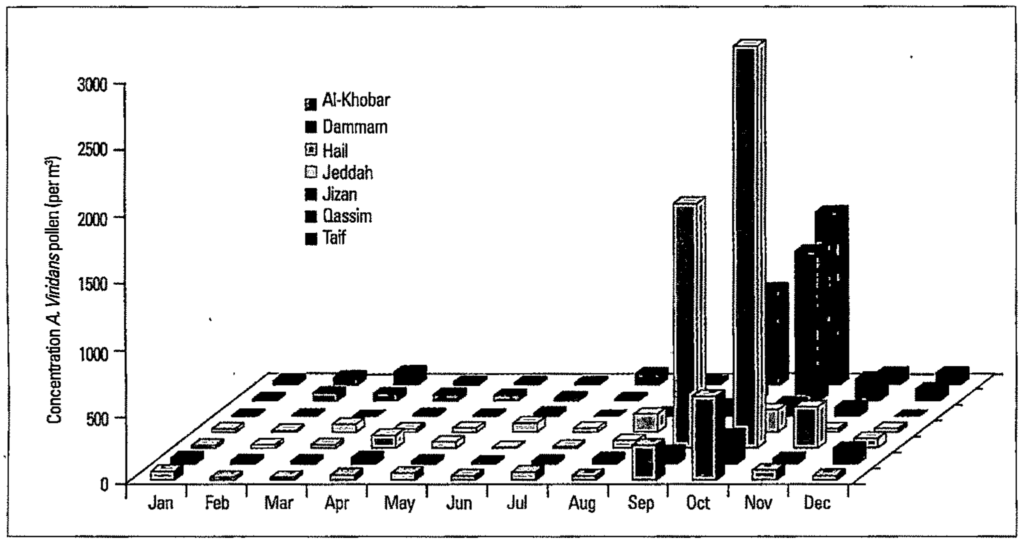

Figure 2. Maximum concentration of airborne *Amaranthus viridis* pollen in seven different regions of Saudi Arabia.

1289/m^3 in Taif, 1115/m^3 in Qassim, 622/m^3 in Al-Khobar, 212/m^3 in Dammam, 167/m^3 in Jeddah and 96/m^3 in Jizan. The rest of the months had low concentrations of pollen.

DISCUSSION

Pollen from some species of *Amaranthus* weed are known to be highly allergenic[2,3] and consequently commercial diagnostic allergens are available only for three species (*A. spinosus, A. retroflexus, and A. palmeri*) out of approximately 87 species known to exist.[12] Two species of *Amaranthus*, namely *A. retroflexus and A. spinosus* are known to be included in the skin test profile.[2,4] The cross-reactivity of some members of *Chenopodiaceae* and

Amaranthaceae[2,4] and the airborne occurrence of only few species of *Amaranthus* (*A. hybridus and A. spinosus*) has been reported.[5,7,8] There have been efforts to include *A. viridis* in the skin prick test (SPT) profile (prepared indigenously) in some parts of the world.[7,9] However, there has been neither a detailed study related to the allergenicity of *A. viridis* pollen and no commercial antigen of *A. viridis* is available. The current study is the first detailed report on airborne prevalence, and the seasonal and diel periodicities of *A. viridis* pollen grains. As such, the study provides a basis for further biochemical and allergological investigations of *A. viridis* pollen in relation to other species in different parts of the world.

The data presented from seven different regions using volumetric methods clearly show that *A. viridis* is the most dominant airborne pollen type contributing greatly to the total weeds pollen catch during August to November in all regions (late summer to early winter in Saudi Arabia). The data revealed that *A. viridis* pollen constituted a maximum of 96% of the total pollen count in Hail, followed by Al-Khobar (89%), Jeddah (87%), Qassim (85%), Taif (84%), Dammam (83%) and Jizan (61%). In addition, the data also showed that *A. viridis* pollen are present in the airspora throughout the year with distinct seasonal variations in its occurrence. Despite regional differences (coastal, agricultural to hilly resorts), *A. viridis* emerged as the most dominant pollen type with a peak in September and October. Although *A. viridis* is known to flower throughout the year, the above-mentioned period (August to November) may be considered the main flowering season and consequently these months may be clinically more relevant for sensitive individuals.

The diel periodicities of *A. viridis* pollen concentrations for all sites averaged over a year had a mid-day to early evening maxima. The data show, at least for four sites, a clear pattern of mid-day to early evening maxima. For the other three sites, because of low concentration, no such trend was clear. As no record of diel periodicities of *A. viridis* is available from other countries, comparison of our data is not possible at this stage. The maximum concentrations of *A. viridis* pollen reached a peak in October (3000/m^3) and in September (1867/m^3). The cross-reactivities amongst weeds pollen are well known, but when clear seasonal and diurnal trends of a particular pollen species are obtained[12] there should be no doubt to include such allergenic extract(s) in the diagnostic profile.

We conclude that airborne *A. viridis* pollen is the most prevalent pollen during August to November in the outdoor environment of Saudi Arabia. The diel periodicities of *A. viridis* pollen showed a clear pattern of mid-day to early evening maxima (diurnal pattern). *A. viridis* pollen displayed a seasonal pattern with higher concentrations during August to November reaching up to 3000/m^3 in October. Allergenicity to *A. viridis* pollen is likely to be more prevalent or to be more suspected during the period August to November when the pollen grains are prevalent in the air. Hence, diagnostic tests should include *A. viridis* antigens in the diagnostic profile of allergens for diagnosis of patients suffering from allergic symptoms during this above-mentioned period. It is also recommended that further biochemical and immunological studies be conducted to confirm its allergenic impact in Saudi Arabia. The cross-reactivities amongst some weeds pollen are well known, but the most prevalent type should be included in the diagnostic profile instead of depending on cross-reactivities.

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original article

Brain MRI findings in infants with primary congenital glaucoma

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BACKGROUND: Congenital glaucoma appears in the first months of life, eventually at birth. Isolated congenital glaucoma is characterized by minor malformations of the irido-corneal angle of the anterior chamber of the eye. Clinical manifestations include tearing, photophobia and enlargement of the globe appearing in the first months of life. Imaging technology such as optical coherence tomography and measurement of central corneal thickness may play an important role in the assessment of children with suspected or known glaucoma. However, no MRI findings of the CNS in patients with primary congenital glaucoma (PCG) were reported in the literature. The purpose of this study was to investigate MRI findings of the brain in infants with PCG.

METHODS: We reviewed the radiological, histopathological and clinical characteristics of infants with primary congenital glaucoma. The records of 17 patients with PCG were reviewed and the MRIs of the brain and associated manifestations were analyzed.

RESULTS: Three patients with PCG had abnormal MRI findings suggesting agenesis of the corpus callosum. Two infants had delayed myelinization of the brain.

DISCUSSION: Significant abnormal optic nerve excavation and increased corneal diameters in 2 patients with delayed myelinization may suggest that intraocular pressure can be more striking and more severe, revealing a close relationship with PCG and abnormal myelinization in the white matter. Studies with more patients are needed to confirm these results.

Congenital glaucoma appears in the first months of life, sometimes at birth. Isolated congenital glaucoma is characterized by minor malformations of the irido-corneal angle of the anterior chamber of the eye. The cause of congenital glaucoma is the presence of an obstacle to aqueous humor outflow and the treatment is primarily surgical. Congenital glaucoma occurs in 1 of 10 000 births in Western countries and the frequency is higher in some countries (especially in the Middle East). Heredity is autosomal recessive, and the genes involved are CYP1B1, GLC3A and GLC3B.[1]

Clinical manifestations include tearing, photophobia and enlargement of the globe, which appear in the first months of life. Primary congenital glaucoma (PCG) is characterized by elevated intraocular pressure (IOP), enlargement of the globe (buphthalmus), edema, and opacification of the cornea with rupture of Descemet's membrane, thinning of the anterior sclera and atrophy of the iris, an anomalously deep anterior chamber, structurally normal posterior segment except for progressive optic atrophy, and photophobia, blepharospasm, and excessive tearing.[2] Typically, the diagnosis is made in the first year of life. Depending on when treatment is instituted, visual acuity may be reduced and/or visual fields may be restricted. In untreated cases, blindness invariably occurs.[3]

The treatment of congenital glaucoma is primarily surgical and appears as an emergency, since the corneal opacity can dramatically increase in a few days or hours. Interventions aim to facilitate the aqueous humor outflow in the irido-corneal angle towards the Schlemm's canal and the subconjunctival space. Goniotomy consists of introducing a needle in the anterior chamber to open the opposite side of the angle. Trabeculotomy creates a communication between Schlemm's canal and the anterior chamber. Trabeculectomy consists of opening the anterior chamber, under a scleral flap, to produce an aqueous humor outflow towards the subconjunctival space.[4]

Imaging technology such as optical coherence tomography and measurement of central corneal thickness may play an important role in the assessment of children with suspected or known glaucoma.[5] However, no MRI findings of the CNS in patients with PCG were reported in the literature. Based on this information, we decided to evaluate our experiences in a group of infants with PCG in a multicenter study. In the present study, we retrospectively reviewed MRI findings of the brain in the infants with primary congenital glaucoma. We focused on the signs and symptoms of clinical manifestations in patients with PCG who had abnormal MRI findings. To the best of our knowledge, this is the first patient series reporting MRI findings of the brain in patients with PCG.

METHODS

The authors reviewed the medical records of 17 infants with PCG seen between 2003 to 2006. We identified a cohort of infants who were diagnosed with PCG in the first month of life and presented to the pediatric neurology and/or opthalmology clinic within the first 6 months of life. We reviewed the clinical records over a 3-year span for all infants who were diagnosed with glaucoma in the Pediatric Neurology Clinic in the Department of Pediatrics, School of Medicine, Gaziantep University, Gaziantep, Turkey and the Pediatric Department of the Eye Clinic in Bielefeld, Germany.

Complete ophthalmic examination was done, including assessment of the intraocular pressure, gonioscopic examination of the filtration angle and examination of the cornea under magnification. Traditional comprehensive evaluations were conducted under anesthesia, and some patients were also safely sedated with chlorohydrate without influencing the IOP. We usually obtained pressure readings with the Perkins applanation tonometers (Keeler, London, UK), the Tono Pen, and the Schiotz tonometers. After a complete neurological evaluation, brain images were requested for all patients.

Seventeen infants diagnosed with PCG had been ascertained and enrolled in the present study. The medical history of all participants was taken in the form of a questionnaire. A comprehensive eye examination by an experienced ophthalmologist, and/or a complete neurological examination by pediatric neurologist were done. Glaucoma was diagnosed and classified as primary infantile, aphakic, syndrome-related, and secondary glaucoma. Patients with IOP associated with other ocular or systemic anomalies such as megalocornea, high myopia, congenital idiopathic edema of the cornea, corneal dystrophic conditions, and corneal opacification secondary to corneal dystrophies or abnormalities of metabolism were excluded from the study.

A diagnosis of glaucoma was established by having at least 2 of the following criteria: 1) repeated IOP measurement over 21 mm Hg, 2) cupping of the optic nerve consistent with glaucoma, 3) increasing corneal diameter, and 4) an excessive myopic shift in the refractive error. The IOP was considered to be in "good control" if it was 19 mm Hg or less and was considered to be in "poor control" if it was 20 mm Hg or more.

Patients with glaucoma were excluded if they had 1) a history of cataract surgery, 2) various conditions that might predipose to development of glaucoma such as rubella, anterior segment dysgenesis or persistent hyperplastic primary vitreous, 3) a syndrome associated with glaucoma, or 4) glaucoma related to systemic problems.

RESULTS

Five of the 17 patients with PCG had abnormal MRI findings. We identified 3 infants with agenesis of the corpus callosum and 2 infants with delayed myelinization.

DISCUSSION

Primary congenital glaucoma is present at birth, but its manifestations may not be recognized until infancy or early childhood. It is characterized by improper devel-

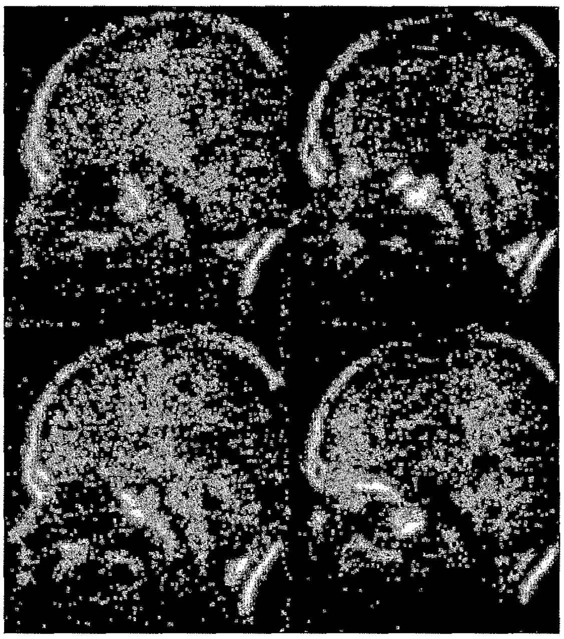

Figure 1. Midline saggittal T-1 weighted MR images showing the medial hemispheric sulci coursing all the way in a radial fashion. The trigones, occipital horns and temporal horns of the lateral ventricles are variably dilated as a result of the agenesis of the corpus callosum.

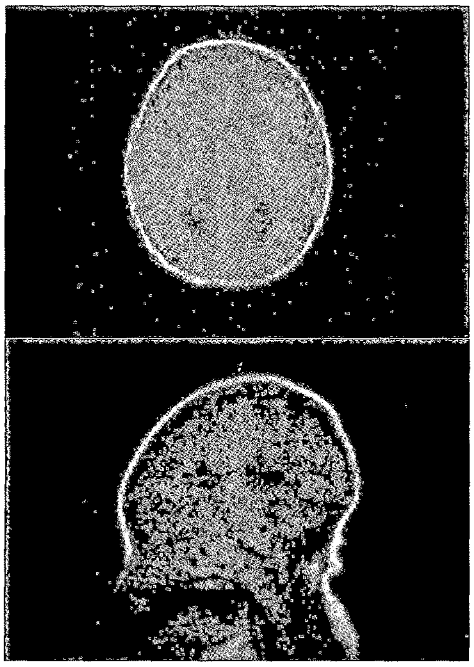

Figure 2. Axial T-1 MRI demonstrating parallel prominent lateral ventricles, which are a typical finding for agenesis of the corpus callosum. The midline saggital T-1 weighted images show that the frontal horns are vertically oriented. The third ventricle is continuous with the interhemispheric fissure and extends somewhat higher than normal between the lateral ventricle.

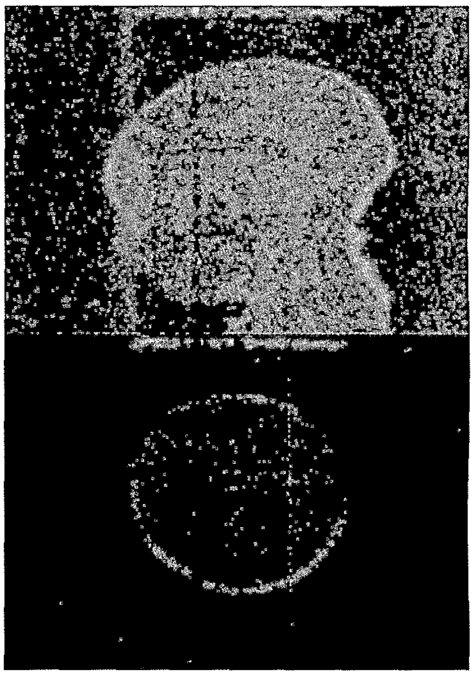

Figure 3. The midline saggittal T-1 weighted MR image is quite characteristic in patients with agenesis of the corpus callosum. Axial T-1 demonstrates enlarged posterior horns and lateral ventricles in parallel alignment. The posterior horns have a characteristic shape that has been described as being similar to the wings of a bird. The third ventricle is continuous with the interhemisperic fissure both superiorly and anteriorly. The lateral ventricles tend to be parallel instead of showing their normal lateral position

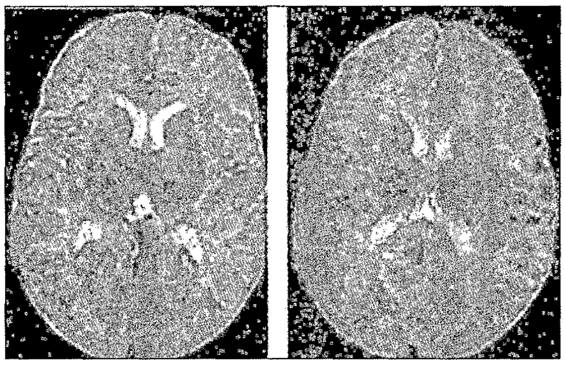

Figure 4. T-2 weighted MRI of 6 month old infant shows rostral progression of the maturation of the internal capsule. The anterior limbs of the anterior capsule are not well myelinated. Isointensity of the cortical gray matter and subcortical white matter, resulting in difficulty in the identification of structural abnormalities at this age suggest delayed myelinization of the white matter.

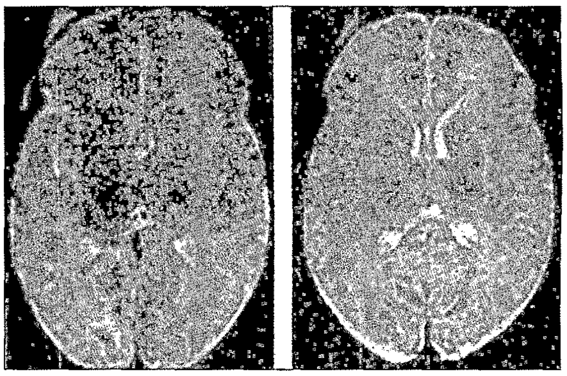

Figure 5. Axial T-2 weighted MRI of a 3-month-old infant showing low signal intensity in the posterior aspect of the posterior limb of the internal capsule, the ventrolateral thalamus and the perirolandic gyri of the cortex. Some low signal peripheral to the frontal horns of the lateral ventricle represent residual germinal matrix. The T-2 weighted images correspond more closely to the MRI of a 1-month-old infant.

opment of the eye's aqueous outflow system, leading to increased intraocular pressure, with consequent damage to ocular structures, resulting in loss of vision. Although the disease is relatively rare, the impact on visual development can be extreme.[6] Early recognition and appropriate therapy of glaucoma can significantly improve the child's visual future. The classic triad of manifestations, any one of which should arouse suspicion of glaucoma in an infant or young child, includes epiphora, photophobia, and blepharospasm.[7]

The purpose of this study was to investigate MRI findings of the brain in infants with PCG. We reviewed the radiological, histopathological and clinical characteristics of infants with primary congenital glaucoma. The records of 17 patients with PCG were reviewed and MRIs of the brain and associated manifestations were analyzed. Three of them with PCG had abnormal MRI findings suggesting agenesis of corpus callosum. Two infants had delayed myelinization of the brain.

Three infants with agenesis of the corpus callosum had PCG and agenesis of the corpus callosum, and significant decreased vacuoles adjacent to the wall of the Schlemm's canal. This may be one of the primary causes of increased IOP.[8] One of these patients had abnormal pupillary enlargement, .which was easily detected, and suggested aniridic pupils on initial examination. One infant with a corneal haze for a week had resolution of corneal cloudiness.

MRI findings in 2 patients showed delayed myelinization. In these 2 infants with PCG, corneal diameters were large (11.5 and 12 cm, respectively). When glaucoma is diagnosed in an infant, the optic nerve head is usually abnormal. Variable cupping is present, usually annular in form, with nasalization of vessels and preservation of the well-vascularized rim. It is believed that increased intraocular pressure affects the optic nerve head much more rapidly in the pediatric population.[9,10] In this study, optic nerve excavation is even more significant in an infant with delayed myelinization of the brain.

The significant abnormal cup/disc ratio (optic nerve excavation) and increased corneal diameters in these 2 patients with delayed myelinization may suggest that intraocular pressure can be more striking and more severe, revealing a close relationship between PCG and abnormal myelinization in the white matter.

An abnormal MRI finding, such as delayed myelinization of the white matter, may also contribute important clinical findings in PCG, including the degree of intraocular pressure, which can determine the prognosis of the infant's vision. We believe there appears to be a relationship between glacuoma and delayed myelinization, although this study had few patients and the findings are not statistically significant due to the limited number of patients. Nevertheless, in the medical literature, this is the first retrospective chart review to report the presence of abnormal MRI findings in infants with PCG. Further studies with larger numbers of patients are needed to confirm these results.

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Pattern of abnormal Pap smears in developing countries: A report from a large referral hospital in Saudi Arabia using the revised 2001 Bethesda System

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BACKGROUND: Reports describing the frequency and pattern of abnormal Pap smears in developing countries using the revised Bethesda system for Pap smear are few. We studied the pattern of cervical intraepithelial lesions and carcinoma detected in Pap smears of Saudi females in the western region of Saudi Arabia using the revised system.

METHODS: All cervical Pap smears reported in the Department of Pathology of King Abdulaziz Medical City, Jeddah, from 1 January 1998 to 31 August 2005 were reclassified according to the revised system with age ranges identified.

RESULTS: Of 5590 sufficient smears, 261 (5%) were identified as abnormal and were further classified as atypical squamous cells of undetermined significance (ASC-US) (103 cases, 40%), atypical squamous cells of high grade (6 cases, 2%), low-grade squamous intraepithelial lesions (LSIL) (56 cases, 22%), high-grade squamous intraepithelial lesions (HSIL) (31 cases, 12%), glandular cell abnormalities (30 cases, 11%) and invasive squamous cell carcinoma (21 cases, 9%). The ASC-US/SIL ratio was 1.9%. Invasive adenocarcinoma accounted for 14 cases (4%) with a similar age range as invasive squamous cell carcinoma.

CONCLUSION: Although this study showed a lower incidence and a wider age range of cervical epithelial cell abnormalities than others published internationally, the results emphasize the need for a well-organized cervical screening program supplemented by larger national studies on the pattern of cervical abnormalities in this country. The information provided in this study will encourage use of the Pap smear as a screening method for cervical cancer in developing countries.

Cervical cancer continues to be a major cause of morbidity and mortality among the female population worldwide, representing the second most common cancer in females with 500 000 news cases and 280 000 deaths each year.[1-3] In underdeveloped countries such as Latin America and Southeast Asia it is considered the leading cause of cancer mortality in women.[1-3] Since the introduction of the Pap smear in the 1940s, the incidence of cervical cancer has dropped dramatically, especially in countries with well-established cervical screening programs such as the USA where it is considered the sixth most common cancer in women with 13 000 cases of invasive carcinomas and 55 000 cases of carcinoma in situ diagnosed annually.[4] In Saudi Arabia, cervical cancer ranks as the eighth most common cancer in females with a mean age of 53 years.[5]

Standardization of Pap smear reporting using the Bethesda system[10] unified various overlapping terminologies and hence improved the diagnosis and management of these lesions. Reports describing the frequency and pattern of abnormal Pap smears in developing countries, particularly Saudi Arabia, using the revised Bethesda system are very few. For this reason the current study was conducted to explore the pattern of epithelial cell abnormalities detected in Pap smears in females of the western region of Saudi Arabia using the Bethesda system and to correlate the findings with published national and international data, in an effort to help improve the utilization of the Pap smear as a screening tool for cervical cancer in our region.

METHODS

We conducted a computerized data retrieval of all cervical Pap smears reported in the department of Pathology of King Abdulaziz Medical City, Jeddah, a large tertiary hospital and oncology referral centre in the western region of Saudi Arabia, in the period from the beginning of January 1998 to the end of August 2005. Adequate smears were first identified. A smear was considered adequate when all needed clinical information was present, including appropriate labeling of the slide, adequate sampling of the transformation zone and optimal preservation of the slide. All adequate cervical cytology smears were reviewed and reclassified according to the revised 2001 Bethesda system of Pap smear reporting (Table 1), into negative for intraepithelial lesions or malignancy or positive for epithelial abnormalities. Under the category of negative for intraepithelial lesions or malignancy the number and percentage of unremarkable (negative) smears and smears showing inflammatory/reactive smears were identified. Smears positive for epithelial cell abnormalities were identified and further classified following the 2001 Bethesda system. In cases of ambiguous diagnoses, the cytology slides were retrieved and reviewed on a multihead microscope by a senior cytotechnoogist and a cytopathologist especially assigned to review these cases using the above mentioned system. The total number and percentages of each abnormal Pap smear category were identified and correlated with the patient's age.

Table 1. The revised Bethesda 2001 system (abridged) for cervical Pap smear reporting.[12]

SPECIMEN ADEQUACY
- Satisfactory for evaluation (*note presence/absence of endocervical/ transformation zone component*)
- Unsatisfactory for evaluation . . . (*specify reason*)
  - Specimen rejected/not processed (*specify reason*)
  - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

GENERAL CATEGORIZATION (*Optional*)
- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality
- Other

INTERPRETATION/RESULT
- Negative for Intraepithelial Lesion or Malignancy
  - Organisms
    - *Trichomonas vaginalis*
    - Fungal oganisms morphologically consistent with *Candida* species
    - Shift in flora suggestive of bacterial vaginosis
    - Bacteria morphologically consistent with *Actinomyces* species
    - Cellular changes consistent with herpes simplex virus
  - Other non-neoplastic findings (*Optional to report; list not comprehensive*)
    - Reactive cellular changes associated with
      - inflammation (includes typical repair)
      - radiation
      - intrauterine contraceptive device
    - Glandular cells status posthysterectomy
    - Atrophy
- Epithelial Cell Abnormalities
  - Squamous cell
    - Atypical squamous cells (ASC)
      - of undetermined significance (ASC-US)
      - cannot exclude HSIL (ASC-H)
    - Low-grade squamous intraepithelial lesion (LSIL)
      - encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
    - High-grade squamous intraepithelial lesion (HSIL)
      - encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
    - Squamous cell carcinoma
  - Glandular cell
    - Atypical glandular cells (AGC) (*specify endocervical, endometrial, or not otherwise specified*)
    - Atypical glandular cells, favor neoplastic (*specify endocervical or not otherwise specified*)
    - Endocervical adenocarcinoma in situ (AIS)
    - Adenocarcinoma
- Other (*List not comprehensive*)
  - Endometrial cells in a woman ≥40 years of age

AUTOMATED REVIEW AND ANCILLARY TESTING (*Include as appropriate*)

EDUCATIONAL NOTES AND SUGGESTIONS (*Optional*)

RESULTS

In the computer database we identified a total of 5746 cervical pap smears received and reported in the Department Of Pathology at King Abdulaziz Medical City (KAMC), Jeddah, in the period from January 1998 to August 2005. The study identified 5590 (97.2%) sufficient smears and 156 (2.8%) insufficient smears. The latter cases were excluded from this study. Of the 5590 sufficient smears, 4304 (77%) smears were reported as negative for squamous epithelial abnormalities while 1025 (18%) showed inflammatory/reactive changes (Figure 1). Two hundred sixty-one smears (5%) were diagnosed as positive for cervical epithelial abnormalities. The positive smears were further classified according to the revised 2001 Bethesda system as shown in Figure 2 and Table 2. No endocervical or endometrial cells, favor neoplastic or adenocarcinoma in situ were reported in this study.

DISCUSSION

In Saudi Arabia, cervical carcinoma ranks as the eighth most common cancer accounting for 3.6% of all cancers in females, with a mean age of 53 years.[5] Although many risk factors has been studied as etiologic factors leading to cervical cancer, recently published international epidemiologic and molecular studies confirm beyond a doubt the strong casual relationship between human papilloma virus (HPV) and cervical intraepithelial lesions and carcinoma independent of other risk factors.[6] The WHO has concluded that there is suffi-

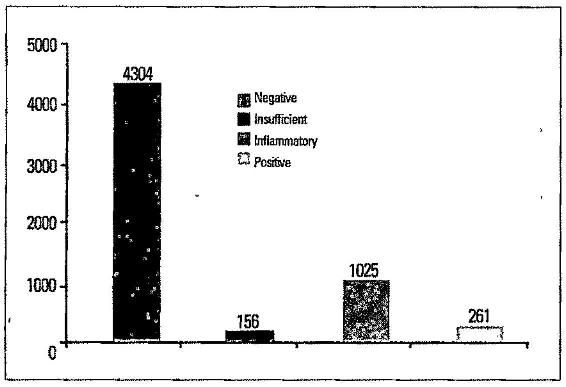

Figure 1. Pap smear diagnosis for 5590 smears from the records of King Abdulaziz Medical City Hospital from 1 January 1998 to 31 August 2005.

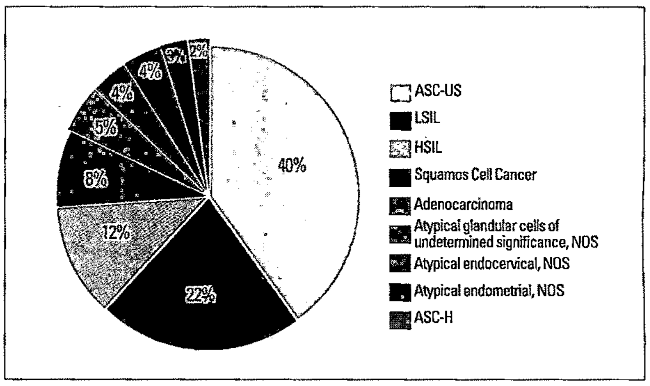

Figure 2. Pattern of epithelial abnormalities in 261 positive Pap smears.

cient evidence to consider HPV as the cause of cervical cancer.[7] Over 100 HPV types have been isolated with more than 15 considered oncogenic (such as type 16, 18, 31, 33, 35, and others) based on their association with malignant lesions.[8]

Over the years, the original Pap smear classification system has gone through many modifications in response to our growing knowledge of cervical carcinoma precursors and our understanding of the rule of HPV cervical carcinogenesis. These overlapping classifications contain several vague terminologies. Poorly defined abnormal smear findings have pushed the medical societies to try to unify different reporting systems.[9] In 1988, the National Cancer Institute adopted the Bethesda system for cervical smear reporting[10] in an attempt to overcome this problem. This system underwent further updates later in 1991.[11] In the year 2001, a revised Bethesda system was introduced[12] to include new technologies such as HPV DNA studies and liquid base cytology. The adequate but limited category in the adequacy component was cancelled and the atypical squamous cells of undetermined significance (ASCUS) category is divided into either atypical squamous cells of undetermined significance (ASC-US) or atypical squamous cells where high grade cannot be ruled out (ASC-H).[12] The United Atates and many other countries use the revised Bethesda classification for both squamous and glandular lesions.

Few reports are present from our region studying the prevalence of cervical cancer and its precursors using the newly revised 2001 Bethesda system. In this study, all abnormal Pap smears received and reported by the pathology department in King Abdulaziz Medical City, Jeddah were retrieved and reclassified following the Bethesda system. Smears studied in this report are of Saudi females since our centre is a strict military and referral hospital for local citizens only. Our results are in agreement with previously published studies from this country,[13-16] showing a lower incidence of abnormal cervical lesions and a wider age range when compared with those from other countries.[17-19] In a previous study from the same hospital,[13] 97 of 3088 Pap smears were reported as abnormal over a period of 7 years. In that study, the findings were as follows: ASC-US (0.45%), LSIL (0.93%), HSIL (0.55%), invasive squamous cell carcinoma (0.13%), AGUS (0.13%), and adenocarcinoma (0.03%).

The percentages of low SIL, High SIL and AGUS categories in the present as well as the above mentioned study from the same hospital were similar, except for a decrease in the percentage in the ASC category (1.84% for ASC-US and 0.1% for ASC-H) and an increase in the incidence of both invasive squamous cell carcinoma (0.37% in the present study) and adenocarcinoma (0.25% in the present study).

Although it may be due to the natural progression of this disease, the increase in the total number of Pap smears with an increased incidence in certain categories and a decreased incidence in borderline categories such as ASC-US is most likely due to the increased rate of referred cancer cases to the recently opened oncology referral centre (opened in the year 2000), the increased awareness of Saudi females of the importance of cervical cancer screening and abidance of cytotechnoogists and cytopathologists to more stringent criteria when submitting diagnoses such as ASC-US.

Edelman et al[17] studied Pap smears from 29 295 females over a period of one year and the Pap smear abnormalities were as follows: 9.9% ASC-US, 2.5% LSIL, 0.6% HSIL and 0.2% invasive cancer. In the same study adolescents with an age range of 13-22 years had a significantly higher rate of LGSIL (low-grade squamous

Table 2. Numbers and percentages of epithelial abnormalities out of the total number of smears (5590) and total number of positive smears (261), including age range and average age using the revised 2001 Bethesda System.

Type of epithelial abnormality	Number of epithelial abnormalities	% of total number of smears (n=5590)	% of positive Pap smears (n=261)	Age range (years)	Average age (years)
ASC-US	103	1.84	40	19-65	42
ASC-H	6	0.1	2	36-70	53
LSIL	56	1	22	29-47	38
HSIL	31	0.55	12	18-67	42.5
Squamous cell carcinoma	21	0.37	9	30-88	59
Atypical endocervical cells, NOS	10	0.17	4	25-75	50
Atypical endometrial cells, NOS	9	0.16	3	22-80	51
Atypical glandular cells, NOS	11	0.19	4	26-89	57.5
Adenocarcinoma (endocervical, endometrial)	14	0.25	4	27-78	52.5
Total	261	4.63	100		

NOS: Not otherwise specified

intraepithelial lesion). The compared to the present study, a comparable number of HGSIL (high-grade squamous intraepithelial lesion) and low number of invasive carcinoma could be related to early detection of abnormal cervical lesions by well established cervical screening programs. In another study from Brazil 18 22 441 Pap smears were examined over a period of 5 years (October 1997-October 2002) and results showed that low-grade lesions were more common in women aged 15-30 years while high-grade lesions were more common in women aged 25-45 years. Patients older than 40 years had the greatest incidence of invasive cancer. Although a similar age range difference between low- and high-grade lesions is seen in the present study confirming the well-established natural history of cervical carcinogenesis, all grades of abnormal cervical lesions were seen in slightly older age groups when compared to the two previous studies, most likely due to late detection of such lesions, usually as a part of either post partum follow up or investigation of a gynecologic complaint.

In our study, The ASC-US category accounted for 40% of all abnormal smears, ASC-H for 2% of all abnormal cases and the atypical glandular cell diagnosis (AGC) including AGUS, NOS as well as atypical endocervical and endometrial cells (NOS) for a total of 11% which compares favorably with other local[13-16] and international figures.[19,20]

In the last decade several new techniques have been developed such as thin-layer cytological preparations and hybrid capture testing for HPV DNA.[21,22] Thin prep cytology, approved by the FDA in 1996, is based on collection of the cervical cell sample in a vial containing a special liquid media. Several studies[22] showed that the thin prep method of sampling results in a significant increase in cytological diagnosis of cervical smear precursors and in an increased percentage of adequate smears as compared with the conventional method of Pap smearing. Although clear recommendations for the use of HPV DNA testing in cervical cancer screening are still not available and data is still insufficient to justify the use of HPV DNA testing as a primary method of cervical cancer screening, the cost effectiveness as well as ability to incorporate the value of a positive HPV test into the management of the screened patient should be studied.[21] In one study by Kaufman et al[23] 1128 women with two readings of either LGSIL or ASCUS on Pap smear received colposcopy, biopsy and HPV DNA testing. The detection of high-risk DNA HPV poorly predicted the likelihood of finding CIN 2 or 3 on biopsy. The sensitivity of HPV testing was only 28% for women with ASCUS and only 58% for women with LGSIL.

In June 2006, the FDA 24 approved Gardasil, a vaccine targeted against HPV type 6 and 11 which accounts for 90% of genital warts and HPV type 16 and

18, which accounts for 70% of cervical cancer. Whether the vaccine can be used effectively in prevention of cervical cancer in this country is yet to be determined. More research is needed to unmask the definite etiological factors for cervical cancer and whether a cause-effect relationship between HPV and cervical intraepithelial lesions and cancer can be established in our country.

Based on the data regarding the incidence of abnormal cervical lesions outlined in the present as well as the previously published local studies and reports,[13-16] health and social organizations in this country should cooperate to build a well-organized national cervical screening program. Key elements for the establishment and success of such a program include increased public awareness, especially in young females about the importance of cervical screening in prevention of cervical cancer, the availability of financial coverage as well as standardization of protocols used in diagnosis and management of these lesions by health professionals. It is recommended that different parties including gynecologists, family physicians and midwives as well active community members initiate such programs. These parties should be aware and work hard to overcome several obstacles that may be faced during the implementation of such programs such as poor education among females from rural areas and small villages as well as the presence of some cultural restraints in those places which prohibit full access to the target groups of the population.

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original article

Cognitive functions in euthymic patients with bipolar disorder

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BACKGROUND: Recent studies have focused on the nature of cognitive dysfunction in bipolar patients. The purpose of the current study was to investigate cognitive performance of individuals with bipolar disorder compared to healthy control subjects during a well-established euthymic period.

METHODS: The sample consisted of 27 bipolar euthymic patients and 21 control subjects. Verbal and visual memory performance, attention, executive functions and psychosocial functions were evaluated for each participant.

RESULTS: Bipolar patients showed significant attentional deficit and executive dysfunction and also poor performance on verbal and visual memory tasks compared to the controls. Illness duration and lifetime total episode number and previous episode with psychotic features was associated with worsened performance on attention, executive and memory tasks. Psychosocial functioning was not associated with cognitive deficit.

CONCLUSIONS: The present study showed persistent cognitive impairment on inhibitory control and selective attention as well as poor performance on verbal and visual memory tests in a group of bipolar euthymic patients. The impaired neuropsychological performance was associated with duration of illness, total number of episodes per lifetime, and previous episodes with psychotic features. Attentional dysfunction seemed to be a trait abnormality for the sample studied.

Bipolar disorder is a recurrent illness with significant disability and heterogeneous outcomes.[1] The view that patients with bipolar disorder make a full recovery between episodes of illness has been widely accepted despite a lack of systematic investigation. In bipolar patients, deficits in executive function, psychomotor skills, and memory have been reported.[2,3,4,5] It has been established that deficiencies in cognitive functions may persist after clinical recovery or in remitted patients and prevent patients from attaining an optimal adaptation in their daily lives.[6-9] Recently, studies focused on the nature of cognitive dysfunction in bipolar patients by increasing body of evidence come from the studies performed on patients in the euthymic state.[3,4,10-14]

In a sample of 41 patients studied during euthymia, Ferrier et al. described poorer performance on executive function in euthymic bipolar disorder patients, regardless of outcome.[7] Further studies have confirmed the presence of cognitive impairment in euthymic patients with bipolar disorder, including reports of reduced performance on tasks verbal memory, cognitive flexibility, psychomotor speed and visuospatial ability.[3,4,10,14-16] Patient age, duration of illness, personality characteristics, treatment and the existence of psychotic symptoms were found to affect cognitive functions.[7,17-19] Recent studies have emphasized that longitudinal studies are required to elucidate the association of cognitive dysfunction with the onset and progression of bipolar disorder.[3,20,21] The purpose of the current study was to compare the cognitive performance of our own sample of patients with euthymic bipolar disorder with healthy controls. Conducting the study during a well-defined euthymic period in our sample provided for exclusion of the effect of residual mood symptoms as far as possible. We expected that the results of the present study might guide to us in future studies as a baseline definition of our group with clinical correlates.

PATIENTS AND METHODS

Twenty-seven euthymic patients (19 female, 8 male), diagnosed with bipolar disorder according to DSM-IV criteria were recruited from a patient sample routinely followed at the Mood Disorder Clinic of the

Department of Psychiatry in Pamukkale University Hospital.[22] All patients who met the inclusion criteria and gave consent enrolled to the study. The healthy controls were 21 subjects (16 female, 5 male) chosen among employees and relatives or acquaintances of the hospital staff working in clinical and administrative areas. The patients did not differ significantly from controls in age, gender and educational level (all P>.05). Subjects with bipolar disorder were observed in the outpatient setting for two months to ensure euthymia before the experimental procedures were administered. Subjects were included in the study if they: (1) met the diagnostic criteria for DSM IV bipolar disorder euthymic phase[22]; (euthymia was defined as having a Hamilton Depression Scale score below 7 and a Bech-Rafaelsen Mania Scale score below 6 for two consecutive monthly assessments,[23,24] just before cognitive testing, (2) had not received ECT within the last year, (3) showed no evidence of systemic or neurologic illnesses that might affect cognitive performance, (4) had no present alcohol or drug abuse or history, (5) were aged between 20-55 years, (6) had a basic educational level of at least 5 years or schooling, and (7) were able to give consent. All the subjects (patients and controls) were right-handed, according to the Turkish version of the Edinburg Handedness Inventory.[25] Comorbid psychiatric disorders (i.e. anxiety or substance abuse) were not present in the patient group at the time of testing, as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders.[26] Also, controls had no prior psychiatric history and had no first-degree relatives with affective disorder. Additional clinical information (age of onset, duration of illness, number of episodes, history of mania with psychotic features, and ongoing treatment) was recorded (Table 1). Hamilton Depression scores and Bech-Rafaelson Mania scores of the patients are also presented in Table 1.

Table 1. Demographic and clinical variables in the bipolar and control groups.

Variables	Bipolar group (n=27)	Controls (n=22)	Statistics
Female, n (%)	19 (70.4)	17 (77.3)	
Male, n (%)	8 (29.6)	5 (22.7)	χ^2=0.203, P>0.05
Age (years), mean (SD)	31.81 (11.17)	34.13 (11.38)	z = -0.562, P>0.05*
Education (years), mean (SD)	10.00 (3.56)	10.45 (3.69)	z = -0.653, P>0.05
Clinical characteristics			
Age of onset (years), mean (SD)	22.59 (8.79)		
Chronicity (years), mean (SD)	9.55 (7.79)		
Total episode number, mean (SD)	5.56 (4.25)		
Previous episode with psychotic features			
Present, n (%)	11 (40.7)		
Absent, n (%)	16 (59.3)		
Treatment			
Lithium, n (%)	15 (55.6)		
Sodium valproate, n (%)	9 (34.3)		
Atypical antipsychotics, n (%)	3 (11.1)		
HRSD-17,* mean (SD)	2.55 (1.69)		
BRMAS,* mean (SD)	2.33 (2.01)		

HRSD-17: Hamilton Rating Scale for Depression, BRMAS: Bech- Rafaelsen Mania Scale *Mann Whitney U test

Each subject was evaluated with a range of cognitive tests in a fixed order: digit span, Verbal Memory Processes Test (VMPT), visual reproduction tests, Stroop Color Word Test (SCWT), Wisconsin Card Sorting Test (WCST) and delayed verbal and visual memory task. Cognitive testing lasted approximately 2 hours with a break halfway. Trained neuropsychology personnel administered all tests. All participants were tested individually. The cognitive evaluation for memory included verbal and visual tests. The verbal tests included the VMPT, an analogue of the Rey Auditory Verbal Learning test in the Turkish language, which was developed by Oktem and Tanor.[27] It uses a 15-word list that is read to the subject ten times. The VMPT provides measures of learning (i.e., registration and acquisition, acquisition being a measure of increase in registered items over trials) and short-term recall, delayed recall, and delayed recognition and intrusion. Visual memory was examined by the Visual Reproduction (VR) Test developed by Wechler and used as a subtest of the Wechsler Memory Scale. This test includes 4 different designs cards. Each design is shown for ten seconds. Following each exposure, subjects draw what they remember of the design. A delayed recall trial is given following a 30-minute delay.[28]

Executive functions and attention were assessed using the Digit span, Digit subtest (Wechsler Adult Intelligence Scale) in which the subject repeats a fixed random series of numbers of increasing length in direct order (digits forward) and in reverse order (digits backward). In addition to auditory attention and short-term retention capacity, this test assesses the ability to manipulate the information in verbal working memory. Raw scores for direct and reverse order were calculated.[28] The Stroop test (Dotrill format) was used to evaluate selective attention, the ability of attentional set shifting and response inhibition. Two trials, one in which reading focuses on color words printed in ink of different colors, and the other requiring naming of the printed colors. For each part, both the time to complete and the number of errors were recorded.[28] WCST was used to examine persistence, strategic planning, category shifting, mental control, and organization.[29] Psychosocial functioning was assessed according to DSM-IV GAF (Global Assessment of Functioning) scale with 0-100 scores.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version (version 10.0) on a PC. Initial data screening using the Leven test for equality of variance indicated that a number of variables had non-normal distributions and a small sample size. Therefore, statistical analyses were performed using the non-parametric Mann-Whitney U test. This method does not assume the asymptotic distribution of a test statistic, and is therefore reliable regardless of the size, distribution, sparseness, or balance of the data. The Mann-Whitney U-test is reported alongside the corrected significance level for each cognitive performance index. The difference between patients and control groups with regard to categorical variables were tested by the Chi Square test. The relationship between cognitive performance and clinical variables were examined by non-parametric correlation analysis (Spearman correlation analysis). All reported P values are two-tailed.

RESULTS

Socio-demographic variables (gender distribution, age, educational status) were not different between bipolar and control group (Table 1). For verbal memory, there were significant differences across the groups in total learning scores on the VMPT, with the bipolar group performing worse than the controls (13.55±1.8 vs. 14.68±0.77, respectively, P=0.007) (Table 2). Delayed free recall scores of patients were also significantly lower than in the control group. Bipolar patients showed more intrusion (false named words) than controls. Delayed recognition (free+cued) scores were not different between bipolar patients and controls. For visual memory, accurate recall of the figure in both short- and long-term memory scores was lower in the patients when compared to controls (P<0.05).

For attention and executive functions, the bipolar group showed poor performance on digit forward compared with controls but there were no significant differences on digit span backward in the digit span test. Color-word interference scores were found to be higher for the patients when compared to controls on the SCWT (P=0.004). There was no significant difference between patients and control groups in terms of WCST findings (P>0.05).

The lifetime total episode number showed significant correlation with poor performance on the verbal memory (delayed free recall) and visual memory task (Table 3). The color-word interference on the Stroop test was positively correlated with illness duration, and lifetime total episode number.

To investigate the influence of a previous episode with psychotic features after clinical remission we compared the cognitive test performance of patients with and without a previous episode with psychotic features and controls. To perform these analyses we preferred non-parametric variance analyses (Kruskal Wallis anal-

Table 2. Results of cognitive measures for the bipolar (n=27) and the control group (n=21).

Cognitive measures	Bipolar group Mean (SD)	Control group Mean (SD)	Z	*P*
Digit span (attention)				
Forward	5.11(0.80)	5.71 (1.10)	-1.802	0.03
Backward	4.14 (1.32)	4.52 (0.92)	-1.622	0.10
Verbal Memory Prosses Test				
Learning	111.48 (22.74)	124.59 (15.20)	-2.31	0.02
Delayed free recall	12.48 (2.40)	13.77 (1.30)	-2.38	0.02
Delayed recognition (free+cued)	15.00 (0.0)	15.00 (0.0)	0.00	1.00
Intrusion	1.92±1.59	0.90 (1.06)	1.67	0.01
Visual Reproduction Tests				
Short-term memory	10.00 (2.84)	12.72 (1.88)	-4.04	0.0001
Long-term memory	8.62 (3.81)	12.59 (2.08)	-3.74	0.0001
Stroop Color Word Test				
Color-word interference	59.37 (31.08)	39.00 (12.81)	3.09	0.004
Spontaneous correction score	2.25 (2.31)	1.13 (1.61)	1.92	0.06
Wisconsin Card Sorting Test				
Categories achieved	3.96 (2.15)aite	4.72 (1.63)	-1.37	0.17
Number of perseverative responses	27.48 (33.91)	18.40 (16.47)	1.14	0.25
Percent perseverative errors	17.88 (20.29)	13.77 (11.01)	0.85	0.39
Percent conceptual level responses	54.88 (32.37)	59.90 (18.70)	-0.64	0.52
Failure to maintain set	0.81 (1.41)	0.90 (1.06)	-0.25	0.79

*Mann-Withney U test

Table 3. Correlations between selected clinical variables and cognitive measures in the bipolar group.

Cognitive measure	Age	Duration of illness	Lifetime total episode number
Verbal Memory Process Test			
Learning	-0.238	-0.354	-0.371
Delayed free-recall	-0.207	-0.164	-0.386*
Delayed recognition	-0.218	-0.257	-0.260
Intrusion	-0.115	-0.006	-0.077
VR (Visual Reproduction)			
Short-term memory	-0.166	-0.172	-0.592**
Long term memory	-0.236	-0.319	-0.443*
Stroop Color Word Test			
Color-word interference	0.397*	0.448**	0.410*
Spontaneous correction score	0.117	0.213	0.423*

*$P<.05$, **$P<.01$, Spearman correlation analysis

Table 4. Comparison of cognitive test performance in patients with a previous episode with psychotic features (n=11), without psychotic features (n=16) and controls (n=22).

Tests	Groups	Mean±SD	χ^{2}*	P*
Stroop Color Word Test				
Color-word interference	Psychotic	71.27±0.61		
	Non-psychotic	51.18±29.57	13.509	0.001
	Control	38.33±12.73		
Spontaneous correction	Psychotic	3.09±2.25		
	Non-psychotic	1.68±2.24	7.412	0.025
	Control	1.19±1.63		
Visual Reproduction Test				
Short-term memory	Psychotic	9.81±3.15		
	Non-psychotic	10.12±2.70	14.093	0.001
	Control	12.80±1.88		
Long-term memory	Psychotic	8.63±4.31		
	Non-psychotic	8.56±3.57	16.505	0.001
	Control	1266 ±2.10		

*Kruskal-Wallis analysis of variance

ysis of variance) due to the unequal and small sample size in each group and non-homogeneity of variance. These analyses revealed significant group differences on the SCWT and visual memory performance (Table 4). We conducted additional analyses to determine which mean was different via pairwise comparisons for these variables (Mann Whitney U test). The later analyses showed that the patients with a previous episode with psychotic features exhibited worse performance on the SCWT and visual memory performance test than controls. On the other hand, the psychotic group differed from the non-psychotic group with respect to only impaired SCWT performance. The illness duration and lifetime total episode number were not significantly different between psychotic and non-psychotic group. The rates of the patients maintaining lithium and sodium valproate treatment were not different between two groups.

To examine the influence of mood stabilizing drugs we compared the cognitive test performances of the patients receiving lithium and sodium valproate. We excluded patients receiving atypical antipsychotics because of small sample size (n=3). We found no significant differences between the cognitive performance of the patients receiving lithium and sodium valproate ($P>0.05$).

In the assessment of psychosocial functioning, the mean GAF score for the bipolar group was 67.66±6.201. GAF scores were negatively correlated with intrusion scores on VMPT ($r=-0.532$, $P<0.01$, Spearman correlation test). The performance on the other cognitive test was not correlated with GAF scores or with illness duration and total episode number.

DISCUSSION

The present study indicates that selective cognitive dysfunction is present in patients with bipolar disorder in the euthymic state. We found that bipolar patients performed worse than control subjects on attention, verbal learning (memory) and visual memory tasks. Our results for executive function measures presented a two-dimensional feature: impaired performance on selective attention and inhibitory control (on SCWT) and preserved performance with respect to ability to establish, maintain and change set, and cognitive flexibility (on WSCT).

The main verbal memory deficit of our study group was characterized by impairments to learning, delayed free recall, and an increase in intrusions. Recent studies have reported that euthymic patients with bipolar disorder showed cognitive deficits on a task of verbal learning and memory.[3,4,14,17,30,31] Delayed recognition scores were not different between bipolar patients and controls in our study group; this finding implied that our bipolar sample tended to show impairment to memory secondarily, in terms of an attentional deficit rather than a true memory retention (storage) or learning deficit. Bipolar patients showed a higher tendency to confabulate in verbal learning task compared with controls. In our opinion, this may be considered as an extension of attentional-executive dysfunction on SCWT, which requires an ability to inhibit a prepotent response tendency.

We also found that visual memory function was impaired in our patients both in short- and in long-term memory. As in our study, some studies have reported non-verbal memory impairment in euthymic bipolar patients.[6,16,32] As reported by Deckersbach et al euthymic bipolar patients showed impaired performance in immediate recall on the Rey-Osterreith Complex Figure Test.[32] Authors have suggested that non-verbal memory problems in these patients are mediated by poor use of non-verbal organization strategies during encoding, but these problems do not appear to reflect deficits in retention of information. Our tendency is to think in the same direction, as expected impairments of immediate visual memory possibly lead to poorer performance on delayed visual recall, and therefore the major problem appears to be the impaired immediate memory process, which is closely related to the attentional process.

Our euthymic patients also showed impairment on the digit span forward and Stroop tests than controls, but they did not differ with respect to WCST performance. The SCWT, especially owing to time pressure, is considered as more specifically focused on attentional domain, while the WCST is considered a measure of executive function, including abilities in strategic planning, organized searching and shifting cognitive set without time pressure. The WCST is more specific for assessment of executive function. Previous studies on the cognitive function of bipolar patients have included patients with different mood states ranging from an acute episode to relative remission and to euthymia.[3-8,19,31,33] Some of these studies have described poorer performance on executive function in euthymic bipolar disorder.[3,4,7,10,14,16,19] On the other hand, Rossi et al and Rubinsztein et al found no significant impairment of executive function in euthymic patients.[12,34] These discrepant findings may be explained by the differences in the samples as well as the variety of measures to assess frontal executive functions across studies. Generally, impaired executive functions have been described in older euthymic patients (39 to 52 years old), in those with a longer duration of illness (13 to 24 years) and more recurrent mood episodes (11 to 24) than our sample.[3,4,10,19,31] Our sample consisted of younger bipolar patients (mean age, 31 years) having a short duration of illness (mean, 9.5 years) and fewer episodes (mean, 5.56) than previous samples. Therefore, as a group our bipolar patients may be considered free of the deteriorative effects of long-standing illness. How can we explain the partial impairment of executive function, predominantly attentional domain, in our sample? Recent studies have suggested that attentional performance may a viable putative endophenotype or trait characteristic for bipolar disorder.[20,35] Burdick et al have studied the longitudinal stability of cognitive performance in bipolar versus schizophrenia probands.[35] They have found that many cognitive domains constantly impaired in schizophrenia and bipolar patients showed constant attentional deficit whereas improvement on executive and memory function improved over time.

We found that the lifetime total episode number, longer duration of illness and the presence of psychotic symptoms in previous episodes significantly correlated with impaired performance on memory and attentional domains. Most of previous studies have reported that patients with a greater number of episodes and longer duration of illness suffer greater cognitive decline as do bipolar patients with psychotic features.[3,12,14,19,31,36] Such associations have generally been thought of as indicating a progressive disease process. Our results have also confirmed these associations for a relatively young and less chronically ill patient sample.

Recent studies have focused more on the negative effect of cognitive dysfunction on psychosocial functioning.[3,4,14] In the present study, we have failed to find such a correlation, but we found only a limited negative effect on verbal memory tasks. The small sample size in our study, compared with others, may have contributed to the relatively well preserved cognitive functioning and reduced chronicity in our patients. Longitudinal studies may help to clarify this issue.

In conclusion, the euthymic bipolar patients in our study exhibited persistent cognitive impairment on selective attention, inhibitory control, verbal memory and learning tests, and these impairments were associated with a longer illness period, recurrent mood episodes and an episode history with psychotic features. However, some limitations of the study could affect the results. Medication effects are a methodological dilemma for euthymic patients, given that the majority of patients are medicated with various mood stabilizers, antidepressants, and antipsychotics, alone or in combination. It is clearly difficult and perhaps unethical to investigate drug-naive/medication-free patients and for this reason there are few and limited data on drug-free patients.[15,37] Even though other studies have reported that medication at the time of testing did not influence the cognitive evaluation, we cannot exclude the possibility that mood stabilizing medication could have influenced the cognitive testing in this patient group.[31,38,39] However, we found no association between mood stabilizing drugs and cognitive performance. Nevertheless our results indicating important cognitive impairment in the euthymic patients with bipolar disorder should taken with caution due to the small sample size. A longitudinal study with a larger sample size and more detailed assessment of attentional abilities could have made our results more reliable. The selective attention deficit and impaired attentional set shifting on time dependent task that may reflect trait abnormalities in bipolar disorder appear to be the most considerable results of the present study. However, this conclusion requires confirmation by further longitudinal studies.

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original article

Interaoperative use of epidural methylprednisolone or bupivacaine for postsurgical lumbar discectomy pain relief: A randomized, placebo-controlled trial

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BACKGROUND: Many patients with lumbar disc surgery experience postoperative back and radicular pain, delaying hospital discharge and resumption of normal activity. Some surgeons have used intraoperative epidural corticosteroids and local anesthetics to decrease pain following surgery for a herniated lumbar disc. Controversies still exist regarding the benefits of these drugs. The present study was meant to compare the effects of the intraoperative administration of epidural methylprednisolone and bupivacaine with that of normal saline (placebo) in lumbar disc surgery for postoperative pain control.

PATIENTS AND METHODS: One hundred fifty patients with single level herniated nucleus pulposus (L4-L5 or L5-S1), which was refractory to 6 weeks of conservative management, were divided randomly in three groups. A standard hemipartial lamimectomy and discectomy was performed on all patients. At the end of the surgery, before the closure of fascia, 40 mg methylprednisolone with 3 mL normal saline for group 1, 2 mL bupivacaine 5% with 2 mL normal saline for group 2 and 4 mL normal saline for group 3 were instilled onto the epidural and exposed nerve root. Postoperative back and radicular pain intensity was assessed by a visual analogue scale (VAS) before and at 24, 48, 72, and 96 hours after surgery.

RESULTS: There was no significant difference in back and radicular pain intensity between the three groups.

CONCLUSION: Intraoperative administration of epidural methylprednisolone or bupivacaine does not relieve postoperative back and radicular pain.

Low back and radicular pain, which are common presentations in clinical practice, are frequently caused by disc herniation.[1,2] Lumbar discectomy for herniated nucleus pulposus is one of the most common operations performed on the spine.[3,4] The aim of this therapy is to relieve the pain, but discectomy is painful for many patients.[4] Although clinical and basic knowledge of pain transmission and modulation has grown drastically, most postoperative pains are treated inadequately.[5-8] Postoperative pain delays mobilization and physical therapy, prolongs hospitalization and alters the patient perspective on recovery.[4] Poor pain control has been directly associated with increased complications, including deep venous thrombosis, pulmonary embolism, decreased pulmonary function, infection, myocardial ischemia and postoperative chronic pain.[5] Some clinicians rely on postoperative analgesics, but others use alternative methods, including intraoperative local anesthetics and/or corticosteroids.[9] Current opinion about the efficacy of epidural methylprednisolone and bupivacaine for postoperative pain relief is equivocal. We compared the effect of intraoperative administration of epidural methylprednisolone and bupivacaine with that of normal saline (placebo) in lumbar disc surgery for postoperative pain control.

PATIENTS AND METHODS

One hundred fifty patients (age range, 30 to 50 years) scheduled for surgery because of symptomatic lumbar disc herniation agreed to participate in this randomized, double-blind, clinical trial with placebo control. The study was approved by the ethics committee.

All patients had a clinical presentation and a physical examination consistent with an acute-onset single level (L4-L5 or L5-S1) unilateral herniated nucleus pulposus that was refractory to 6 weeks of conservative management consisting of analgesic and nonsteroidal antiinflammatory drugs. The diagnosis of each patient was confirmed by lumbar magnetic resonance imaging. Patients having motor deficits, spinal or lateral stenosis or previous intervertebral disc surgery were excluded. Patients were randomly assigned by a computer program to one of the three groups with a defined sample size.

All patients were premedicated with diazepam (0.1mg / kg). Anesthesia was induced with 2-3 μg/kg of fentanyl and 3-4 mg/kg sodium thiopental. Orotracheal intubation was facilitated with the administration of intravenous 0.3-0.4 mg/kg of atracurium. Anesthesia was maintained with halothane and 50% nitrogen oxide and 50% oxygen.

A standard surgical procedure consisting of open discectomy and hemipartial laminectomy with unilateral exploration was performed on all patients as follows: skin incision was performed between the L3 and S1 spinous processes. After the incision of the paramedian fascia, the paravertebral muscles were retracted. After identification of the level, hemipartial laminectomy, flavectomy, and discectomy were performed. Before closure of the fascia and subcutaneous tissues, and after hemostasis, 40 mg methyprednisolone with 3 mL of normal saline for group 1, 2 mL of bupivacaine 0.5% with 2 mL of normal saline for group 2, and 4 mL of normal saline for group 3 were flushed into the epidural space and nerve roots. The fascia and subcutaneous tissue were closed after drug administration and the skin was sutured.

All patients and staff involved in postoperative pain management and data collection were unaware of the group to which patient had been assigned. All patients received the same postoperative pain management: 100 mg of meperidine intramuscularly followed 4 hours later by a second dose. Assessment of pain was performed with a 10-cm visual analogue scale (VAS) (0 cm=no pain, 10 cm=worst pain imaginable). Back pain and radicular pain intensity were assessed the day before surgery. It was also assessed at 24, 48, 72, 96 hours after surgery.

The back and radicular pain intensity of the three groups were compared by the repeat measure method using the model "back or radicular pain = Person + Group + Time (Group) + residual" for statistical analysis with Minitab software (version 13). The results are reported as mean ± standard error (SE). A $P < 0.05$ was considered statistically significant. With a confidence and power level of 95%, using the "compare groups" formula, the maximum sample size, based on a standard deviation of 0.82 for methylprednisolone and 0.70 for bupivacaine and a maximum error of 0.55 for each group, was 50 patients.

RESULTS

The three groups did not differ statistically with regard to age, weight, sex, level of surgical discectomy, and length of the surgery (Table 1). There was no significant difference in the severity of radicular pain between the three groups ($P=0.595$) at any particular time point (Table 2). However, the main difference between the three groups was related to time of evaluation ($P=0.0001$). In other words, the longer the post-surgical time is, the less the severity of radicular pain. There was no significant difference in severity of back pain between the three groups ($P=0.948$) at any particular time point (Table 3). However, the major difference between the three groups was related to time of evaluation ($P=0.0001$). In other words, as time passes from surgery, the severity of back pain decreases.

DISCUSSION

The causes of back and radicular pain in patients with lumbar disc herniation are still unclear.[10-13] For many decades sciatica and nerve dysfunction in conjunction

Table 1. The age, sex, operated level, weight and duration of operation for the three groups.

	Mean age (years)	Male	Female	L4-L5	L5-S1	Weight (kg)	Duration of operation (mean)
Bupivacaine	38.16±0.16	20 (40%)	30 (60%)	28 (56%)	22 (44%)	75.1±0.25	70.2±0.48
Methylprednisolone	37.2±0.51	23 (46%)	27 (54%)	26 (52%)	24 (48%)	74.2±0.32	74.1±0.23
Normal saline	38.92 ±0.66	24 (48%)	26 (52%)	29 (58%)	21 (42%)	76.5±0.18	73±0.34
P value	0.144	0.704	0.704	0.828	0.828	0.437	0.418

Values are mean±SD

Table 2. Severity of radicular pain in the three groups at different times.

Time of evaluation	Methylprednisolone	Bupivacaine	Normal saline
Before operation	6.14±0.2	6.28±0.2	6.10±0.19
24 h after operation	2.88±0.22	2.84±0.27	2.76±0.19
48 h after operation	2.56±0.23	2.02±0.18	2.38±0.21
72 h after operation	1.46±0.18	1.34±0.14	1.52±021
96 h after operation	1.04±0.14	1.04±0.11	0.90±0.16
		P=0.595 between three groups	

Values are mean±SD

Table 3. Severity of back pain in the three groups at different times.

Time of evaluation	Methyl prednisolone	Bupivacaine	Normal saline
Before operation	4.14±0.27	4.06±0.31	4.30±0.27
24 h after operation	4.64±0.22	4.88±0.24	4.38±0.21
48 h after operation	3.84±0.17	3.48±0.20	4.08±0.22
72 h after operation	3.22±0.17	3.04±0.16	3.02±0.18
96 h after operation	2.32±0.14	1.04±0.17	2.18±0.14
		P=0.948 between three groups	

Values are mean+SD

with lumbar disc herniation were believed to be solely due to mechanical compression of the spinal nerve roots. In contrast to what was thought earlier, spinal nerve roots undergo functional and histological changes after epidural exposure to nucleus pulposus without any mechanical compression. Thus, nerve root pain and dysfunction probably have a more complex pathophysiology, comprising compression and nerve root inflammation.[9,12-22] Inflammation plays a major role in the evolution of symptoms. The nucleus pulposus contains materials that are inflammatory and neuroexcitatory.[15-18,22-25] The nerve root does not become sensitized or begin to transmit pain signals until an inflammatory process is generated. Once inflammation is established, however, the nerve becomes exquisitely sensitive to pressure, producing pain with even gentle pressure.[15,24] A number of chemical modulators interact to foster the inflammatory cascade and to sensitize nerve endings. Phospholipase A2, an inflammatory mediator, is present at a high level in the human intervertebral disc. It may play a role in painful disc pathology. Pain-related neuropeptides such as substance P or vasoactive intestinal peptide may be released, which then leak from the nucleus through the annulus, sensitizing or irritating the adjacent nerve root. Different proinflammatory substances have been proposed as present in the nucleus pulposus such as tumor necrosis factor alpha, interleukin-1, interleukin-6, nitric oxide, platelet-activating factor, prostaglandin E2, leukotrienes, and reactions by histamine-like substances.[22,25]

In addition to various inflammatory mechanisms, immunological reactions have been suggested. The nucleus pulposus, normally confined within the annulus fibrosus, has no contact with the systemic circulation in the adult. This avascular localization could theoretically give the nucleus the status of a foreign body, not recognized by immunocompetent cells. Therefore, nucleus pulposus has been proposed to possess antigenic properties.[22]

Epidural steroids are commonly used in the treatment of back pain and radiculopathy.[24,26] The mechanism of corticosteroid activity is not yet fully understood.[25] Various modes of the action of the corticosteroids include blockade of phospholipase A2 activity and prostaglandin synthesis,[16,19,21,27-29] membrane stabilization,[16,19,27-29] a reversible local anesthetic effect,[19,21,25] prolonged suppression of ongoing neuronal discharge,[21,28] and inhibition of peptide synthesis or suppression of sensitization of dorsal horn neurons.[21] The safety of steroids and preservatives at epidural therapeutic doses has been demonstrated in both clinical and experimental studies.[29] Methylprednisolone is the least irritating, the most beneficial and the longest acting among corticosteroids.[29]

In a randomized clinical study, Debi et al assessed the effectiveness of epidural methylprednisolone acetate to reduce pain following lumbar disc surgery. They reported significant back pain relief on postoperative days 1, 2, 6 and 14 in the group that received steroids. No difference between the two groups was found 1 year after surgery or when radicular pain was compared.[8] Davis et al showed that intraoperative application of an epidural steroid such as methylprednisolone in a unilateral lumbar discectomy leads to a shorter hospital stay because of less pain and spasm.[30] Lavyne et al reported that epidural corticosteroid administration after microsurgical lumbar discectomy for unilateral disc herniation does not lessen postoperative morbidity or improve functional recovery.[31]

Local anesthetic agents have been widely used in surgical operations to reduce postoperative pain.[9,32] Bupivacaine is a long-acting amide local anesthetic used for analgesia in acute and chronic pain. It has been infused epidurally and intrathecally as a single drug or in combination with other agents.[33] After epidural administration, these drugs need to cross the spinal meninges to reach their site of action.[32] The primary site of action of epidurally administered local anesthetics appears to be the dorsal and ventral spinal root as they exit the spinal column.[5] Epidurally administered local anesthetic drugs block sensory and motor nerve function in a concentration dependent manner so that it is possible to achieve selective sensory blockade without motor block by limiting the concentration of the drug.[5,34] Bupivacaine is a high potency and long duration local anesthetic that can be used safely in the epidural space.[5,35] In a double-blind randomized trial, Milligan et al described 60 patients in whom, based on the VAS score and narocotic use in the first 24 hours after surgery, bupivacaine was beneficial. In another study, bupivacaine was considered to be beneficial because there were significant differences between the groups considering the time of the first postoperative use of narcotic analgesic.[9] An interesting finding is that the combination of corticosteroids and bupivacaine diminished postoperative back pain and opioid usage without complication.[9]

In summary, we report that intraoperative use of epidural methylprednisolone or bupivacaine compared with that of normal saline (placebo) has no beneficial effect on postoperative pain relief during the 96 hours following lumbar disc surgery. According to this study we conclude that the intraoperative use of epidural methylprednisolone and bupivacaine do not have beneficial effects on postoperative pain relief following lumbar discectomy surgery. Therefore, we do not recommend the use of these drugs for postoperative pain control.

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Evaluating "superiority", "equivalence" and "non-inferiority" in clinical trials

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Clinical studies are usually performed with the aim of justifying that a new treatment approach is "superior" to the common standard approach (active control) with respect to benefits. In a general sense, this justification is carried out on the basis of the "null hypothesis significance test" with the *P* value based on this test used for justification. Today, new drugs differ so little from existing ones that factors such as cost and side effects affect the choice of therapy, when the bioavailability of treatment methods are found equivalent. Therefore, the aim of comparative clinical trials has extended beyond showing that a treatment is "superior" and now attempts to show that new treatments are "equal" and "non-inferior" to existing treatments. New approaches have become necessary since the classical null hypothesis approach is insufficient to justify the use of new agents, especially in cases of "equivalence" and "non-inferiority". This new approach to justification makes use of the "clinical equivalence interval", which determines the limits of the differences between specific endpoints that can be regarded as clinically "equal" to the value that was pre-specified based on studies of established therapies. It also makes use of the quantitative-based "confidence intervals" as the criteria for statistical justification. Many analyses can be done confidently when these tools are applied and the data are interpreted correctly.

Clinical studies are usually performed to reach conclusions about the superiority of one treatment over another. The concept of "superiority" might have different characteristics in various contexts. Generally, this justification is carried out using statistical significance tests to reject the "null hypothesis". This brings up the point that failing to show superiority does not mean that there is equivalence.[1] Today, the aims of clinical research exceed simply showing that a treatment is "superior" to the other by clinical effect size. Clinical research also aims to address issues related to "equivalence" and "non-inferiority." If there is no difference between two drugs that are equal in clinical effectiveness but not in other characteristics, such as side effects, costs and ease of use, then these other factors will result in selection of the best drug.[2-5] Therefore, clinical research evaluations are designed to test:

- The superiority of a new initiative (drug or treatment) to an available initiative,
- The non-inferiority of a new initiative to an available initiative,
- The equivalence of a new initiative to an available initiative.

Irving et al stated that when designing a non-inferiority/equivalence trial the investigator intends to show efficacy by demonstrating that a new treatment is as good as or not worse than a known effective treatment by a small predefined margin.[6] However, the classical null hypothesis and the *P* evaluation on the basis of the classical null hypothesis are not enough to justify "equivalence" and "non-inferiority".[2,7,8] New concepts and approaches have been designed to provide reliable justifications in the selection of the most effective therapy. In our review, we will briefly explain these approaches.

Approaches to justification

The typical approach to evaluate the results of a clinical study related to two (or more) comparative sets of quantitative or qualitative data is based on a *P* value obtained through a statistical analysis. The inadequacy of

P values stems partly from theoretical questions about their meaning and interpretation, and also from the fact that they do not in themselves convey adequate information about the size or direction of the effect or the range of possible outcomes.[2,8] Clinical features of the study might result in falsely evaluating differences, which have no clinical importance, as reflecting superiority in the acceptance of the null hypothesis. This point will especially be important in "justifications excluding superiority". The criterion for equivalence determines the difference that will be regarded as "equivalent" to the mean value, denominated by an interval called "Δ", which is determined by the clinician and is predicted-expected-known in a specific clinical situation.[5] For example, if a clinician regards a decrease of only 30 mm Hg as a clinically important difference as opposed to a decrease of 10 mm Hg in the systolic blood pressure, which is predicted as 165 mm Hg, then the "interval for equivalence" is 30 mm Hg. The statistical analysis of comparative clinical trials is generally based on "confidence intervals",[9] and the P value obtained is based on values obtained by previous research. Confidence intervals provide a more reliable comparative measurement of the real difference, which is more interesting and important than a P value. Also, confidence intervals give more detailed information about superiority, equivalence, and non-inferiority than the P value. Therefore, the upper and lower values of the confidence interval can be interpreted as the efficiency of the treatment with a high level of certainty. Thus, the confidence interval demonstrates the size of the effect as well as the lowest and the highest margins of the estimate in addition to evaluating the null hypothesis.[2,8]

Factors other than the statistical analysis are important to consider in judging "equivalence" and "non-inferiority". In this context, the methodological principles that should be used to compare a new initiative with common control initiatives[2,3] are to ensure that equivalence and noninferiority criteria are predefined, to determine the eligible conditions for the study, in which the efficacy of the common control initiative was established, to apply both initiatives under eligible conditions, and to allow sample size estimates to be based on the correct power calculations. Thus, the clinical study, which will include a comparative justification, must have three basic statistical elements apart from the methodological characteristics, whatever its interpretation: the P value for the comparison, confidence intervals, and clinical equivalence intervals.

Justifications for Superiority

The justification for superiority is intended to prove that a new experimental drug is superior to the common control drug. The classical approach is the statis-

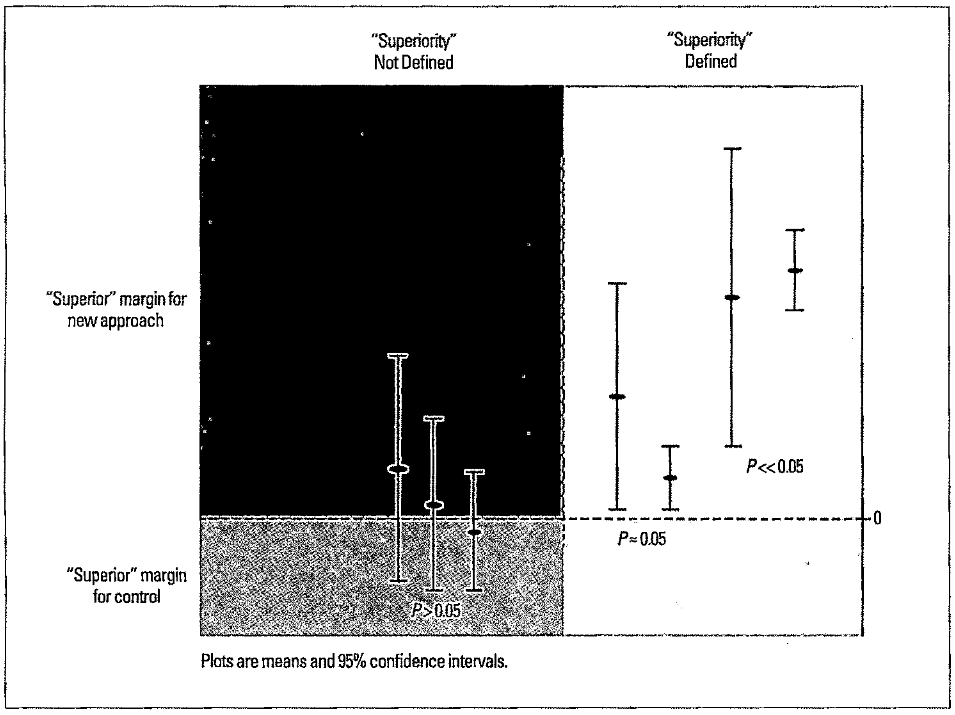

Figure 1. The statistical figuration of the evaluation for "superiority" using the approach of confidence intervals.

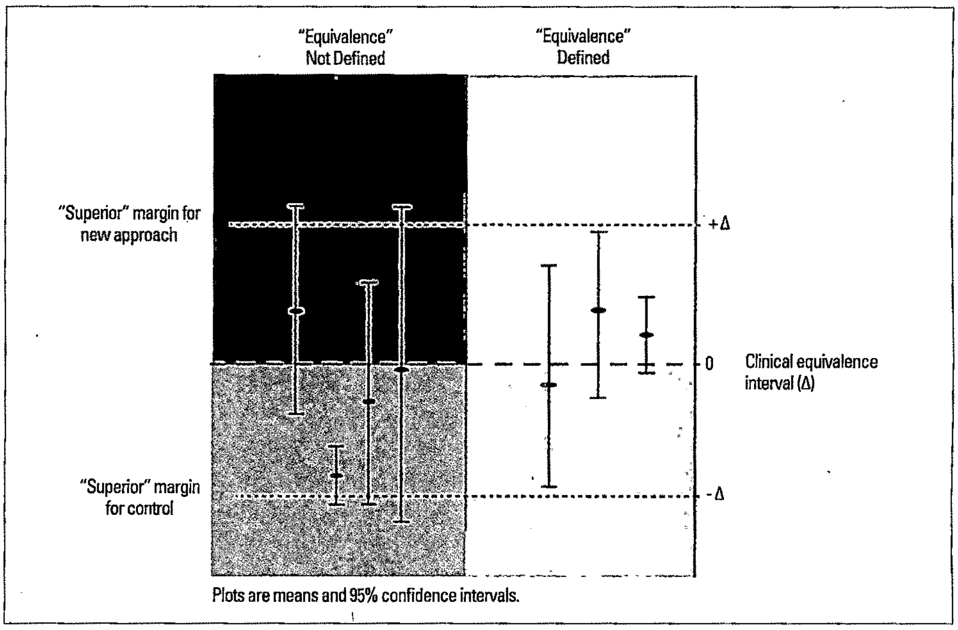

Figure 2. Confidence interval approach and evaluation of the equivalence with "Δ".

tical justification that shows no difference between the clinical effects, including a declaration that the null hypothesis is met. First, once this difference is determined as not equal to "0" through statistical analysis, then the size of the difference to detect whether the effect is clinically adequate or not is estimated. The "real" value for the difference between treatment effects lies within the boundaries of the confidence interval (Figure 1). The "null hypothesis" (no difference between clinical effects) is rejected if the upper bound of the confidence interval for the difference between the test treatment and control is lower than the specified margin.[2] Thus, the two situations given below become equivalent to each other:

- The bilateral confidence interval of 95% for when the difference between the means includes "0"
- Two means are different from each other bilaterally when considered at the 5% level statistically.[5]

Naturally, the significance level can be regarded as different from 5%. If the "clinical equivalence interval" has been used to predict the number of samples at the beginning of the study, the result will be reliable. Yet, the clinician has the right to judge a difference seeming significant within his own criteria.

Justifications for Equivalence

When two drugs are absolutely equivalent it is not possible to find an exact equivalence of the predictive means (or rates) due to the biological variability of the phenomena.[9] Therefore, trials for equivalence are designed to prove the absence of a significant difference between the drugs. Temple at al[2] reported that such drugs would not show superior efficacy in active-control trials, yet equivalence to the active control with respect to efficacy would not have been informative.[10] The evaluation starts with the prediction of the greatest acceptable "clinically identical" difference, and the "clinical equivalence interval". Thus, it is accepted that the differences that exceed this level by occurring more or less than the exact amount are important clinically, and therefore, the clinical equivalence margin is chosen by identifying the clinically acceptable and the greatest difference in the justification for equivalence. If two drugs are equivalent to each other, then the bilateral confidence interval of 95% for the difference of effect between the drugs must cover the area between -Δ and +Δ (Figure 2). In this framework, there are equivalence margins, which can be asymmetrical with respect to zero, and they are determined by the clinician. In studies on bioequivalence, the confidence interval of 90% is accepted as a standard in the evaluation of the two drugs to find out whether their pharmacokinetic criteria means are equivalent to each other or not.[5]

Justifications for Non-inferiority

A noninferiority trial refers to a study in which the primary objective is to evaluate whether the new treatment is not inferior to or as effective as the standard therapy for a particular end point. It is not important

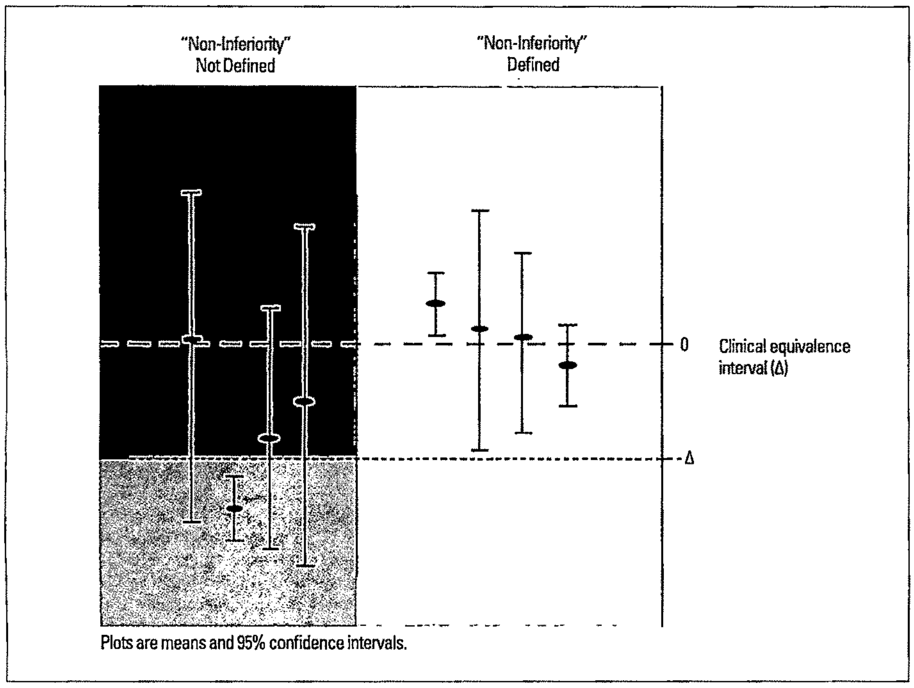

Figure 3. Confidence interval approach and evaluation of the non-inferiority with "Δ".

to establish that the new drug is more effective or has similar effects, only that it is adequate to determine that it is not inferior to the drug to be compared. At this point, the evaluation starts with the prediction of the "clinical equivalence interval (Δ)" and continues by determining the bilateral confidence interval (90% or 95%). However, in this context, only a one-way probability of the difference is investigated. Thus, the confidence interval must extend to the "–Δ" side (Figure 3). The application of confidence intervals in the one-way justification meets the classical null test hypothesis that the difference of treatment effect that is equal to a lower margin of equivalence contrary to the alternative of a difference of treatment that is higher than the lower margin of equivalence level.[12] "Justifications for non-inferiority" might be designed in the same way as justifications for equivalence and cause misinterpretations, especially when the difference in treatment effect mentioned formerly is disregarded.[5,9] In this context, the margin chosen for the justification for non-inferiority cannot be greater than the size of the lowest effect that the control drug is expected to have. The identification of the margin is based on both statistical inference and clinical justifications, and thus, it must reflect the uncertainties within the proof on which the choice is based and it must also protect its place appropriately. If these analyses are carried out properly, the finding that the confidence interval for the difference between the common standard approach (active control) and the new drug excludes the margin, which has been chosen appropriately, might guarantee that the drug has a greater effect than zero. The margin, which has been chosen through projecting the size of the clinically acceptable effect, will probably be lower than the amount proposed with the expected lowest size of the effect of the standard approach.[13]

Conclusion

The chance of finding new treatment methods, techniques, and drugs that are superior to existing ones is so little that the differences between drugs for the same treatment are starting to be based on secondary characteristics such as price, side effects, and ease to use. However, differences based on these factors can only be made after comparing the efficiency of the treatment. Therefore, the aim of many studies is not only justifying that a treatment is superior to another, but also justifying that two treatments are equivalent to each other or that one of them is non-inferior to the other. If the evaluations are carried out on the basis of just simple statistical test results, inadequate or false result justifications might be obtained. It is very important to make the hypotheses with their characteristics clear in this kind of scientific study, as in other scientific research fields. The second important topic is the "clinical equivalence interval", and this concept is mostly identified through sizes of the intervals, which are determined by the clinician. The confidence interval for the difference between the comparative effects of the treatment provides the correct interpretation when it is justified with the other two concepts. The *P* level, which can be reached with classical statistical justifications, has only a certain importance, and it may cause inadequate or even false justifications when it has been evaluated without considering the other concepts that have been mentioned. It is vitally important to justify clinical studies by examining them within the framework of the concepts.

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Congenital intrinsic duodenal obstruction: a review of 35 cases

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Congenital duodenal obstruction is one of the relatively common surgical conditions in infants and children. Over the years, the prognosis of infants and children with this condition has improved markedly, which is attributed to several factors such as early diagnosis, improved surgical techniques, and improved perioperative management, including availability of total parenteral nutrition. Several factors, however, still affect the overall outcome including prematurity, a high incidence of associated anomalies and reoperations.[1,2] The high incidence of associated anomalies, mainly severe congenital heart disease, contributes to the increased morbidity and sometimes mortality.[3] The overall long-term outcome is also affected by the high incidence of Down's syndrome.[2] This report is an analysis of our experience with 35 cases of intrinsic congenital duodenal obstruction with an emphasis on factors affecting the final outcome.

PATIENTS AND METHODS

Over a period of 12 years from 1993 to 2005, a total of 35 infants and children with intrinsic congenital duodenal obstruction were treated at our hospital. Their medical records were retrospectively reviewed for age at diagnosis, sex, gestation, and birth weight, history of polyhydramnios, symptomatology, associated anomalies, and method of diagnosis, treatment and outcome. Extrinsic causes of duodenal obstruction were excluded.

RESULTS

Of the 35 cases of congenital intrinsic duodenal obstruction treated at our hospital, 19 were males and 16 females. Their birth weight ranged from 1.4 kg to 3.8 kg (mean, 2.5 kg). Twelve (34.3%) were premature. The mean maternal age was 23 years (range, 18-34 years). All our patients presented or were referred to our hospital within two weeks of life except for five who presented at 5 months, 3.5 years, 1.8 years, and 1.5 years, and 2 months of age. All five had duodenal diaphragm with a hole, which was the reason for the delayed presentation. Two of them presented with complete duodenal obstruction following the eating of dates with seeds, which resulted in occlusion of the hole in the diaphragm. The remaining patients presented with bile-stained vomiting. Upper abdominal distension was seen in 19 (54.3%) and polyhydramnios was reported in 12 patients (34.3%). Associated anomalies were seen in 23 patients (65.7%) (Table 1). Ten had Down's syndrome (28.6%) and 7 (20%) had congenital heart disease. Six (17%) had rotational abnormalities of the gut including two patients with situs inversus. These two patients presented with bile-stained vomiting immediately after birth and abdominal x-ray showed the classic double- bubble sign, but the stomach was on the right side (Figure 1). The diagnosis of situs inversus was confirmed by preoperative abdominal ultrasound.

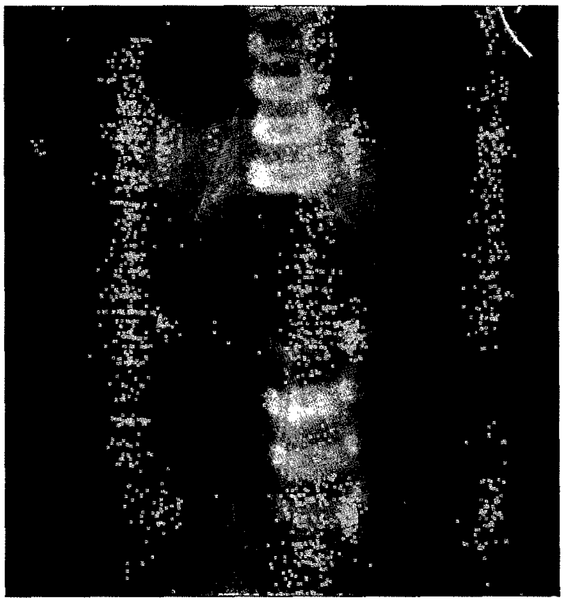

Figure 1. Plain abdominal x-ray showing classic double-bubble sign in a patient with situs inversus and congenital duodenal obstruction.

Table 1. Associated anomalies.

Associated anomaly	No.	%
Down's syndrome	10	28.6
Congenital heart disease	7	20
Malrotation and situs inversus	6	17.14
Congenital pyloric atresia	2	5.7
Duplication cyst	2	5.7
Anorectal malformation	2	5.7
Pelvi-ureteric junction obstruction	2	5.7
Arterio-venous malformation	1	2.9
Congenital leukemia	1	2.9
Esophageal atresia an tracheoesphageal fistula	1	2.9
Cystic left kidney	1	2.9
Syndactly	1	2.9
Hypoplastic left thumb	1	2.9
Meckel's diverticulum	1	2.9
Eventration of right diaphragm	1	2.9

Table 2. The operative procedures.

Operative procedure	No. of patients
Duodeno-duodenostomy	13
Duodeno-duodenostomy and appendecectomy	5
Excision of duodenal diaphragm and duodenoplasty	7
Ladd's procedure + excision of duodenal diaphragm and duodenoplasty + appendecectomy	4
Duodeno-jejunostomy	6

Echocardiography was normal in one and in the other there were features of Fallot's tetralogy. In the remaining four patients, the diagnosis of associated malrotation was made intraoperatively. All had malrotation with Ladd's bands, and in addition, they had intrinsic duodenal obstruction, which was diagnosed intraoperatively. Two had duodenal atresia and four had duodenal diaphragm with a hole. Interestingly, two of our patients had congenital pyloric atresia associated with duodenal atresia at the fourth part of the duodenum. This resulted in a closed duodenal loop with pyloric atresia at one end and duodenal atresia at the other end with accumulation of biliary and pancreatic secretions. This resulted in duodenal perforation in one patient. In both, the diagnosis of associated duodenal atresia was made only intraoperatively. One of our patients had dysmorphic features, esophageal atresia with tracheoesophageal fistula and hydronephrosis. Intraoperatively, this patient had duodenal atresia, annular pancreas and a preduodenal portal vein. One of our patients had eventration of the right diaphragm.

All our patients were operated on and intraoperatively the site of duodenal obstruction was located in the second part of duodenum in 32 patients (91.4%). In two, the site of obstruction was at the fourth part of the duodenum while in the third it was located at the third part of duodenum. The causes of obstruction were duodenal atresia without a gap in 12 (34.3%), duodenal atresia with a gap in 6 (17.14%), duodenal stenosis in 4 (11.43%) and duodenal diaphragm in 13 (37.14%). In 7 patients (20%), there was an associated annular pancreas. The different operative procedures, which are shown in Table 2, were used initially in the series. Subsequently, none of our patients had gastrostomy or a transanastomotic feeding tube as part of their operative management. Fourteen (40%) required total parenteral nutrition. Two of our patients had reduction duodenoplasty to decrease the size of the duodenum. Two of our patients required reoperations, one because of an anastomotic leak and another because of duodenal dysfunction. This patient underwent reduction duodenoplasty and subsequently did well. Four of our patients died giving an overall mortality of 11.4%. In all 4, associated anomalies were the cause of death (Table 3).

DISCUSSION

Congenital duodenal obstruction is an interesting anomaly, both embryologically and clinically. During the fourth to the sixth week of intrauterine life, the duodenal lumen is obliterated by the rapidly growing epithelium. The duodenal lumen than recanalyzes by the twelfth week. Intrinsic duodenal obstruction is thought to result from failure of recanalization or arrest of duodenal growth.[4] This differentiates congenital duodenal atresia from atresia in the rest of the intestines, which result from an intrauterine vascular accident.[5] Congenital duodenal obstruction is divided into intrinsic and extrinsic depending on the etiology.[6] Intrinsic causes include atresia, stenosis and duodenal diaphragm with or without a hole. Extrinsic causes include malrotation with congenital bands, duplication, annular pancreas and preduodenal portal vein. It is not uncommon to find combined intrinsic and extrinsic

Table 3. Causes of death in four patients.

Age	Sex	Associated anomalies	Cause of death
5 days	M	Congenital pyloric atresia, duplication cyst, jejunal atresia.	Immunodeficiency and sepsis
2 days	M	Congenital pyloric atresia.	Immunodeficiency and sepsis
3 hours	M	Esophageal atresia and tracheoesophageal fistula, non-rotation, preduodenal portal vein, annular pancreas, dysmorphic features, intra-uterine growth retardation, hydronephrosis.	Associated anomalies and cardiorespiratory arrest.
5 days	F	Down's syndrome, severe congenital heart disease, prematurity.	Congenital heart disease, prematurity, septicemia

causes of congenital duodenal obstruction in the same patient.[1] This was the case in four of our patients who had malrotation with congenital bands as well as intrinsic duodenal obstruction. The importance of this needs to be emphasized to obviate subsequent morbidity and reoperations, which are not uncommon in patients with congenital duodenal obstruction. Bailey et al, in a large series of 138 infants and children with congenital duodenal obstruction, reported reoperations in 14% for technical reasons, for other atresias that were missed initially and for other unrelated lesions.[1] There was also a surprisingly high incidence (20%) of combined anatomic abnormalities in their series, including a number of infants with both malrotation with bands and duodenal atresia, stenosis, or web.[1] Intraoperatively, it is important to check the patency of the gastrointestinal tract even in the presence of an extrinsic cause of duodenal obstruction. Seven of our patients had associated annular pancreas and two had associated duplication but in all, there was an associated intrinsic duodenal obstruction.

The incidence of associated anomalies with congenital duodenal obstruction is variable.[1-3,7-9] Down's syndrome and congenital heart disease continue to be the commonest anomalies associated with congenital duodenal obstruction. The incidence of Down's syndrome in our series was 28.6%, which is lower than that reported by Akhtar and Guiney.[2] One reason for this is the high proportion of younger mothers in our series (mean maternal age was 23 years) when compared to the Akhtar and Guieny series (mean maternal age was 33 years). Two of our patients had situs inversus in association with congenital intrinsic duodenal obstruction. Situs inversus is a very rare condition with an estimated frequency ranging from 1 in 4000 to 1 in 20 000 live births.[10] It is commonly associated with other serious cardiac and splenic malformation.[11,12] This was the case in one of our two patients who had Fallot's tetralogy. The diagnosis of congenital duodenal obstruction in association with situs inversus can be made on plain erect abdominal x-ray when a reverse double-bubble sign is seen. This can be confirmed further by barium meal and follow-through.

The treatment of congenital duodenal obstruction is standardized. Duodeno-duodenostomy continues to be the treatment of choice. Kimura et al in 1977 described the diamond-shaped duodeno-duodenostomy.[13] None of our patients had the diamond-shaped anastomosis, but there are several reports supporting this type of anastomosis as these patients had earlier oral feeds when compared with the side-to-side duodeno-duodenostomy.[2,13] For those with duodenal diaphragm, we continue to do excision of the duodenal diaphragm and duodenoplasty.[14] We resort to duodeno-duodenostomy only when there are technical difficulties because of the close proximity of the duodenal diaphragm to the ampulla of Vater. Six of our patients were treated with duodeno-jejunostomy. In three patients, this was because of the site of obstruction in the third and fourth parts of the duodenum while in the other three patients it was due to technical operative difficulties. Duodeno-jejunostomy is considered a less physiological procedure when compared to duodeno-duodenostomy, but when the obstruction is located in the third or fourth parts of the duodenum, duodeno-jejunostomy is a more feasible procedure. Gastrostomy was used as part of the operative treatment of congenital duodenal obstruction in four of our patients in the initial series. We agree with others that gastrostomy should no longer be used as part of the management of congenital duodenal obstruction.[2] A transanastomotic tube was used in six of our patients, and like others we no longer use transanastomotic tubes.[2] They tend to recoil back and cause anastomotic disruption.[15] Two of our patients had reduction duodenoplasty due to megaduodenum during the initial operation in one and secondary to duodenal dysfunction postoperatively in the other. We advocate reduction duodeoplasty during the initial operation in patients with megaduodenum.

Our overall survival of 88.6% compares favorably to reports from Western countries.[1,2] This survival rate was in spite of a high rate of prematurity (34.3%) in our series. This is attributed to improved surgical techniques and improved perioperative management, including total parenteral nutrition. Severe associated anomalies, however, continue to contribute to a high mortality. Four of our patients died and associated anomalies were the cause of death. Two of them had associated congenital pyloric atresia and both died because of sepsis secondary to immunodeficiency. When congenital pyloric atresia forms part of the hereditary multiple intestinal atresias it is known to be associated with combined immunodeficiency, which contributes to mortality.[16-18]

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case report

Unusual presentation of internal carotid artery aneurysm in the middle ear

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An aberrant course of the internal carotid artery (ICA) through the middle ear is uncommon. Approximately one percent of the population presents with a dehiscent ICA canal. Embryological malformation of the first and second branchial arches would prevent the formation of the ICA bony covering over the tympanic part of the middle ear.[1] These abnormalities are usually asymptomatic and often diagnosed during ear surgeries.[2] We report a case of unilateral ICA aneurysm in the middle ear. The literature is reviewed and the diagnosis and risks in clinically treating this anomaly are discussed.

CASE

A healthy 25-year-old Saudi female presented to the Otorhinolarnygology, Head and Neck Section of King Abdulaziz Medical City, Jeddah, Saudi Arabia, with left-side hearing loss and no record of otorrhea, tinnitus, vertigo, hemorrhage or otalgia. There was a history of suppurative bilateral chronic otitis media. The patient had undergone a left canal wall-up tympanomastoidectomy three years previously. This same procedure was done two years later to the right side without intra- or post-operative complications.

Otoscopy revealed a dry central residual tympanic membrane perforation in the left ear and an intact graft in the right ear. There was no facial weakness, nystagmus or other ear, nose, and throat abnormalities. Rinne's test was negative bilaterally and Weber's test was lateralized to the left ear. An audiogram showed bilateral mild-to-moderate conductive hearing loss more on the left side with an air bone gap of 20 decibels (dB).

The patient was booked for left revision tympanoplasty. During the operation, after elevation of the tympanomeatal flap, adhesions between the middle ear mucosa and a previously inserted silastic sheet were found. After releasing the adhesions and removing the sheet, severe bleeding was encountered, raising the suspicion of a dehiscent jugular bulb. The middle ear was tightly packed with a *Surgicel* absorbable hemostat, the external auditory canal packed with non-absorbable gauze, and the procedure was aborted. The patient was hospitalized for one week. During this period there were no further episodes of bleeding. The patient was discharged with a new external ear pack, which was to be changed again at a 7-day follow-up visit. Five days after discharge the patient presented to the emergency room with bleeding from the left ear, tachycardia, a normal blood pressure and her hemoglobin had dropped from 13 to 9 g/dL. The external ear pack was extruding and another pack was applied to control the bleeding. The patient went into hypovolemic shock, was resuscitated, and admitted to the intensive care unit (ICU).

The patient developed right hemiparesis and underwent CT imaging the next day with enhancement for the brain and the temporal bone which showed a bilateral intact jugular bulb, a bony rarefaction around left petrous carotid, and a small brain infarction in the left temporal (Figure 1). On the third day an angiography was performed, which confirmed the presence of an aneurysm in the left ICA through the hypotympa-

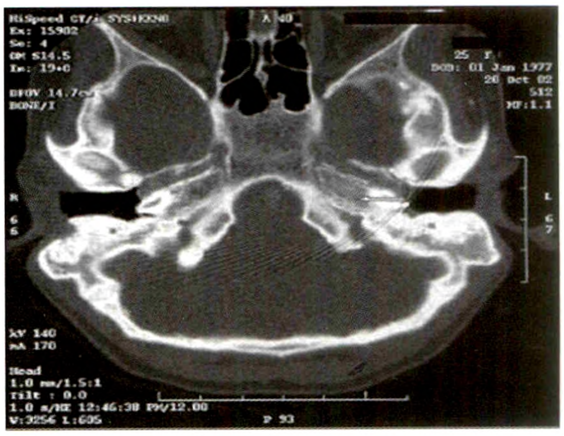

Figure 1a. Axial CT of the temporal bone shows the aneurysm of the internal carotid artery in the left middle ear.

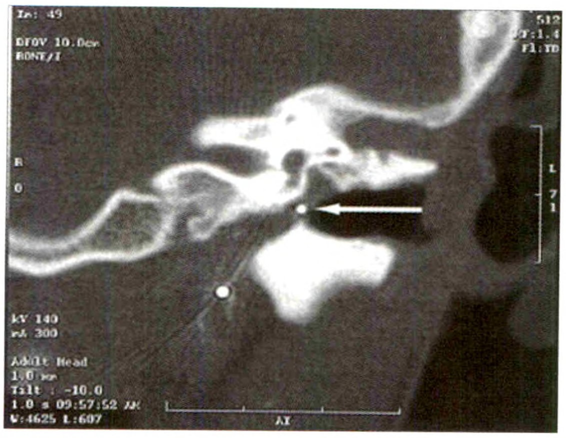

Figure 1b. Coronal CT of the temporal bone shows anomalies around the left petrous carotid artery.

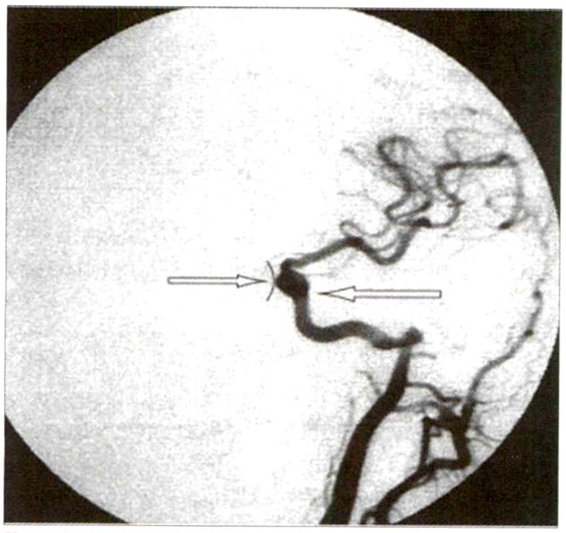

Figure 2. Angiography of the carotid artery shows an aneurysm of the internal left middle ear.

num (Figure 2). Two days later in the ICU, the bleeding stopped, the weakness improved and the patient was transferred to the ward. After six days, the aneurysm was successfully embolized with detachable platinum coil fillings and the patient recovered neurologically.

DISCUSSION

Anomalies of the ICA are very rare and the incidence is difficult to determine. Glasscock et al suggested an incidence of one percent of the population.[3] Cohen and Briant considered the incidence of bone dehiscence over the ICA to be considerably less than reported.[4,5] A review of the literature showed some case reports involving children and adults. Only 42 clinical cases of an aberrant ICA in the middle ear had been reported before 1991. Most cases of intratympanic ICA occurred in women (female:male ratio, 5:1), often occurring unilaterally on the right side (female:female ratio, 2:1). However, it has been reported bilaterally.[6] The present estimate is about 50 published cases.

Normally, the ICA enters the petrous bone medial to the styloid process via the carotid canal, separated from the internal jugular vein by the carotid ridge. The initial vertical segment is anterior to the cochlea and separated from the tympanic cavity by a plate of bone approximately 0.5 mm thick that was possibly cribriform in childhood and may reabsorb in old age. The ICA then turns anteriorly to lay inferior and posteromedial to the eustachian tube, traverses the foramen lacerum, and enters the middle cranial fossa.[2,6]

The precise causes of an aberrant ICA in the tympanic cavity remain unclear.[2] Anomalies of the ICA within the temporal bone include aneurysms and arterial displacement, and both can be either congenital or acquired.[7] Congenital aneurysms are thought to originate from a persistent stapedial artery or the abnormal persistence of embryonic vasculature that may supply enough traction to pull the ICA into the tympanic cavity. This traction may pull or fix the ICA laterally into the middle ear. Proposed acquired causes include head trauma, previous surgery, atherosclerosis, chronic infections, cholesteatoma and malignancies.[6,8]

ICA anomalies in the middle ear represent a diagnostic problem since both symptoms and signs are nonspecific. Patients may be asymptomatic or complain of pulsatile tinnitus, hearing loss, otalgia or aural fullness. Otoscopy may show a vascular bluish-red mass in the anteroinferior mesotympanum–the "rising sun sign". An audiogram usually shows conductive hearing loss while impedance testing may reveal a pulsating tympanic membrane.[1,2] These symptoms and signs are not distinct to ICA aneurysm and could signify vascular anomalies in the middle ear space (Table 1).[6,9] Anomalies of the ICA have a typical appearance on a high resolution CT scan: an enhancing intratympanic mass, with the vessel lying lateral to its normal position, the absence of the bony plate between the hypotympanum and the ICA, and the jugular fossa is separated from the carotid canal by a spur of bone.[10]

Even though it has been suggested that a CT scan alone is sufficient to confirm the diagnosis, it does not always differentiate between a vascular anomaly and a high vascular glomus tumour.[11] Conventional carotid angiography remains a standard reference for diagnosis as it shows the lateral displacement of the vertical segment of the ICA in the anterior/posterior view; it is important in the assessment of vascular supply and

Table 1. Differential diagnosis of a vascular mass in the middle ear.

- Aberrant ICA
- Petrous ICA with aneurysm with dehiscent bone
- Dehiscent jugular bulb
- Glomus tympanicum
- Glomus Tumours
- Cholesterol granuloma
- Persistent stapedial artery
- Other vascular temporal bone lesions

the confirmation of the presence or absence of an aneurysm.[1]

Lapayowker et al described the "vestibular line", which is a vertical line drawn tangential to the lateral most extent of the vestibule.[12] This line indicates the lateral limit of the normal intratympanic ICA. If the artery lies lateral to this line it is considered aberrant. These features can be demonstrated by the less invasive magnetic resonance angiogram (MRA), suppressing the need for conventional angiography.[13] The limitation of MRA relates to the reduced flow of such large aneurysms, and the signal intensity is reduced with limited visualization.[14]

The best treatment of aberrant or aneurysm of the ICA is to avoid manipulation, informing any physician involved in the patient's care of this precaution.[5,6] However, in the case of chronic middle ear infection, surgical techniques to restore the middle ear cavity and to cover the aberrant vessel permanently with a bone graft are advocated by Ruggles and Reed.[15] The surgeon should be aware of the risks of hemiparesis, temporary aphasia, permanent hearing loss or even death. In case of iatrogenic injury during myringotomy or middle ear surgery, immediate treatment should consist of packing of the middle ear with absorbable material such as *Surgicel*, then tight packing of the external canal to control the bleeding. The surgeon should be careful not to damage the middle and inner ear structures as a result of haphazard pack placement or complete occlusion of the ICA by too firm packing, which can lead to neurological sequelae. Additional steps to control hemorrhage include a posterior epistaxis pack or balloon, ICA ligation and balloon occlusion at the middle ear level under EEG monitor as the last resort.[2] The treatment for a confirmed aneurysm would be embolization by filling the aneurysm with detachable platinum coils.[16] The patient should have regular follow up after hemostasis.

Awareness of the existence of vascular anomalies in the middle ear, although they are uncommon, is essential. Any abnormal clinical or radiological findings should be considered suspect. Failure of accurate diagnosis could have disastrous consequences. The preferred method of treatment is avoidance of middle ear manipulation.

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case report

Primary superficial basal cell carcinoma of the nipple

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Most basal cell carcinomas (BCC) occur on the sun-exposed skin of the head and neck regions. Arising from the sun-protected areas is uncommon and the nipple is an exceptionally rare primary site. Since the first full description by Robinson,[1] only 25 cases have been reported in the literature.[2-5] There is no consensus about the treatment of BCCs of the nipple. Ten to 30 percent of BCCs are superficial and occur most frequently on the trunk and the limbs.[6] We report the first case, to our knowledge, of a superficial type BCC in the nipple.

CASE

A 74-year-old female was referred for eczematous changes in the right nipple for several months. She also had no history of insult to the right breast. No pruritis, discharge, ulceration, or pain was noted. Physical examination revealed no axillary lymphadenopathy. Paget disease of the nipple was first considered and an excisional biopsy was performed. Gross examination of the surgical specimen disclosed an ellipse of skin that measured 1.6 × 0.9 × 0.9 cm with attached subcutaneous tissue. On light microscopic examination, the tumor consisted of several foci of superficial lobules of basaloid cells arising from the epidermis into the dermis (Figure 1). All these superficial lobules were confined to the papillary dermis. The tumor cells had round-to-oval nuclei with scanty cytoplasm. Characteristic peripheral palisading of the basal cells was also noted (Figure 2). The final diagnosis was superficial BCC. All the resection margins were free. The post operation course was smooth and uneventful. No adjuvant therapy was done.

DISCUSSION

BCCs arising from the nipple are encountered extremely rarely. Our case was probably the first case of a superficial type BCC reported in the literature. Several variants of BCC have been described, including the superficial type, which occurs mainly on the trunk. Superficial BCC arises as a multifocal proliferation of tumor nests attached to the epidermis, with the characteristic feature of peripheral nuclei palisading.

The exact etiology of BCCs arising from the nipple is still obscure. Of the 25 previously reported cases, 16 were reported in men.[2-5] It has been postulated that the male predominance may be due to a higher amount of sun exposure in this area.[7] All cases are sporadic and no familial aggregation has been observed.

The clinical appearance of BCCs in the nipple is various and differentiating BCC from Paget disease of the nipple, Bowen disease, or other benign breast disease is considerably hard for the clinician. Microscopic examination is usually diagnostic and straightforward without much difficulty.

Calcification was reported as present in BCCs of the

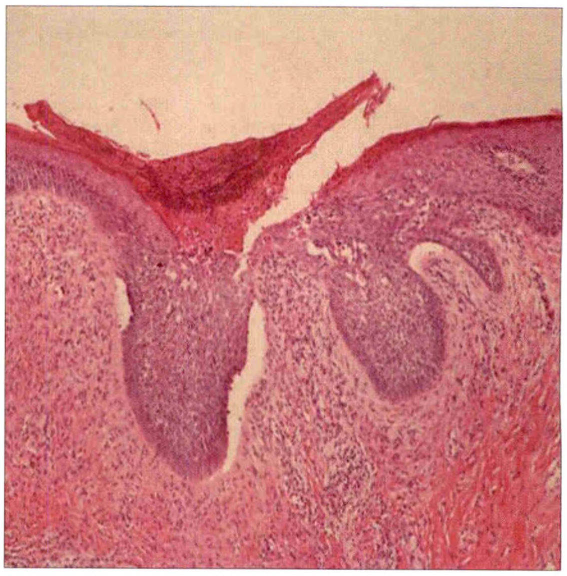

Figure 1. Skin of the nipple shows several superficial islands of basaloid cells arising from the epidermis into dermis. Note: all these superficial lobules are confined to the papillary dermis (H&E, ×100).

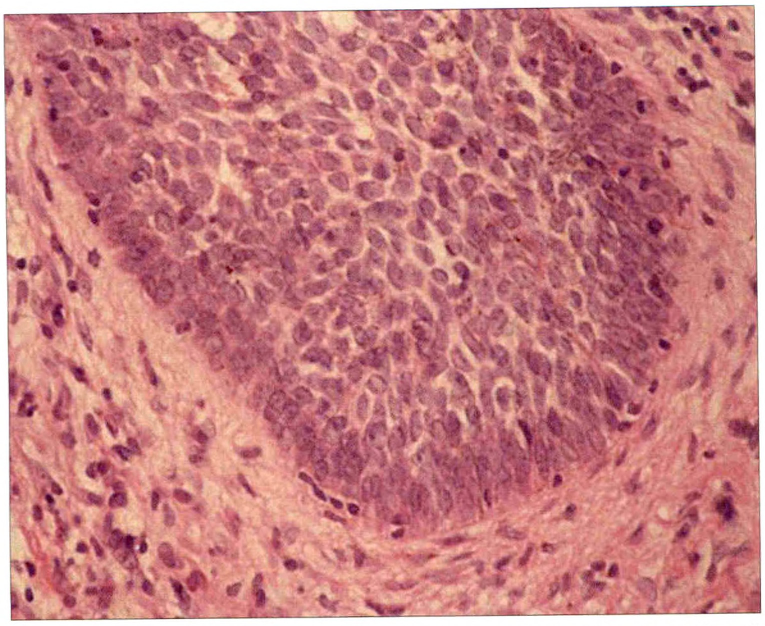

Figure 2. Higher magnification demonstrating the characteristic peripheral palisading of basal cells. (H&E, ×400)

nipple,[8] which may cause diagnostic difficulty because calcification in breast cancer is a well-known phenomenon. Therefore, accurate diagnosis can be difficult based solely on radiological observation. A histological examination is required to make the precise diagnosis.

BCC is a locally destructive tumor that is rarely metastatic. Treatment methods include surgical excision with clear margins, local destruction with radiotherapy, cryotherapy, photodynamic therapy, intralesional interferon treatment, fluorouracil, or imiquinod.[9] Among the 25 cases reported in the literature, 3 patients had axillary lymph node metastasis. The metastatic rate for primary BCCs in the nipple is 12% (3/25), which is much higher compared to a less than 1% metastatic rate from other common sites for BCCs.[10] Due to this increasing rate of metastasis, more aggressive treatment may be needed for the BCCs in the nipple. Wide excision with safe resection margins is required. When axillary lymph nodes are clinically palpable, sentinel lymph node biopsy or axillary lymph node dissection may be considered. Pathologic features of our case revealed a superficial type BCC with a clean resection margin and no obvious axillary lymphadenopathy; therefore, no more aggressive treatment was given but the case was followed up closely.

In conclusion, BCCs of the nipple are an extremely rare neoplasm with more aggressive behavior compared to those that occur outside the nipple. Accurate pathological diagnosis and appropriate treatment modalities with close long-term follow-up are highly recommended in these rarely encountered patients.

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case report

Erythema induratum: What is the role of *Mycobacterium tuberculosis*?

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Erythema induratum (EI) was first described by Bazin in 1861, who attributed the condition to tuberculosis (TB).[1,2] In 1901, Whitfield hypothesized that there were two forms of EI, one of which was related to TB.[3] EI is a tuberculid, characterized by chronic or recurrent tender subcutaneous nodules, which sometimes ulcerate. The lesions typically are located on the lower extremities of adult women.[1,4,5] Most individuals with EI have a positive tuberculin skin test, but rarely have evidence of active TB.[4,8]

EI lesions appear histopathologically as a granulomatous lobular panniculitis and vasculitis, with the affected artery lying in the septum of subcutaneous fat.[4,8-11] Several authors were able to demonstrate *Mycobacterium tuberculosis* DNA by polymerase chain reaction (PCR) in tissue biopsy from EI lesions, which leads to the belief among investigators that *M. tuberculosis* has a role in EI lesions.[9-13] We report two cases of EI and their therapeutic response and review the literature on EI.

CASES

The first case was a 63-year-old Saudi female who presented with a 3-week history of painful left lower limb erythema. There was neither a history of TB nor a family history of TB. On examination, she was had a well-defined 3 × 6 cm indurated ulcer at the medial aspect of the left leg close to the heel. The erythrocyte sedimentation rate (ESR) before treatment was 120 mm/hr and the PPD test was positive. Biopsy showed a chronic, active ulcer associated with focal granulomatous changes, with the inflammation extending to the subcutaneous adipose tissue associated with fat necrosis and thrombotic occlusion of blood vessels. The biopsy result was consistent with EI. Culture for *M. tuberculosis* and PCR were negative. The patient was treated with anti-TB medications (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months and then isoniazid and rifampicin for 4 months. During this period, she showed a dramatic clinical response with gradual decline in the ESR to 39 mm/hr.

The second case was a 35-year-old Saudi female who presented with a one-month history of painful multiple erythemas in both lower limbs. There was no previous history of TB and no family history of TB. On examination she had 9 multiple indurated, painful nodules, variable in size, 7 lesions in the left lower limb and 2 lesions in the right lower limb (Figure 1). ESR was 112 mm/hr and the PPD skin test was positive. A biopsy for this patient showed lobular panniculaitis, with inflammatory changes seen in the subcutaneous fat and in the interface between the reticular dermis and subcutaneous fat, where there was prominent venulitis in the reticular dermis. In addition, granulomatous inflammation was identified in the panniculus and in the reticular dermis. The biopsy result was consistent with EI. *M. tuberculosis* culture and PCR were negative. She was treated with anti-TB medications (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months and then isoniazid and rifampicin for 4 months. She had an excellent clinical response (Figure 2) with a decline in the ESR to 30 mm/hr.

DISCUSSION

EI was described initially by Bazin in 1861.[1,2] Audry, however, challenged the hypothesis that EI has any relation with *M. tuberculosis* in 1898.[14] Whitfield reached the conclusion that there are two forms of EI, one of which was related to *M. tuberculosis*, in 1901.[1,3] Montgomery and colleagues described 72 patients with EI, and most of the patients (85%) were females. A PPD test done on 25 patients was positive in 84%.[15]

Many authors have shown that EI can respond successfully to anti-TB therapy.[16-18] Degitz and colleagues demonstrated that *M. tuberculosis* DNA can be found in the EI lesion by the use of PCR, in 1993. They were able to demonstrate *M. tuberculosis* DNA in skin biopsies using PCR in 5 of 7 patients with EI.[19] Several authors have shown that EI lesions can be associated with other types of active TB like tuberculous lymph-

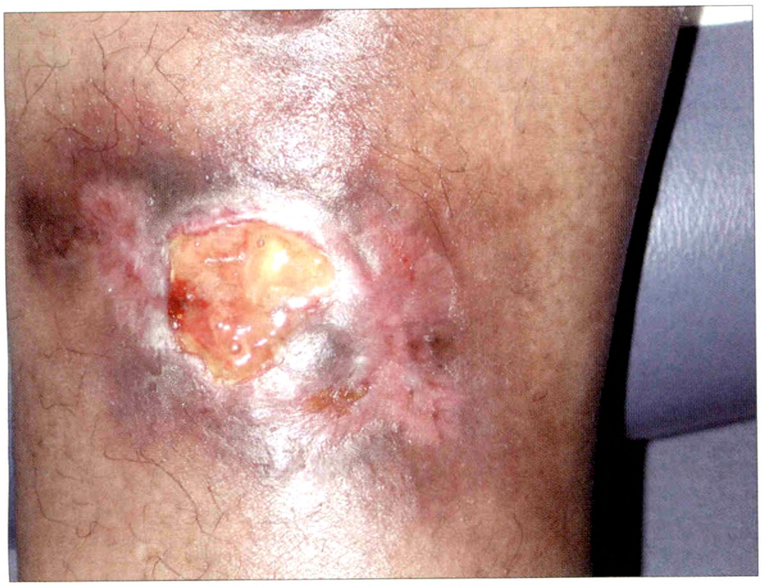

Figure 1. Ulcerated erythema induratum on presentation.

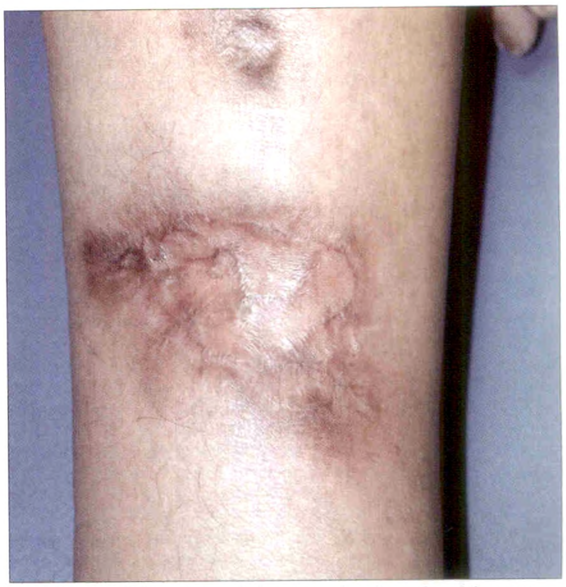

Figure 2. Healed erythema induratum after 6 weeks of therapy.

adenitis,[6,20] pulmonary tuberculosis,[21] renal tuberculosis,[22] endometrial tuberculosis,[23] and tuberculosis of the nasopharynx.[24]

A review of the medical literature shows that EI lesions can present as a primary lesion[1,4,5,8,15,18,19] or a secondary skin disease to other active tuberculosis.[20-24] Distler and colleagues reported a case with panniculitis for 30 years,[25] and Ollert and colleagues reported two cases of chronic EI for 10 years.[8] All of these cases have responded successfully to anti-TB therapy. Both of our cases who had chronic EI lesions diagnosed histologically have successfully responded to 6 months of anti-TB therapy. However, both of our cases did not have caseating granuloma on the histopathology of their skin biopsy and we were not able to diagnose a tuberculous origin of their lesions microbiologically. Also, *M. tuberculosis* DNA was negative on the PCR in both cases.

Most of the published studies support the use of *M. tuberculosis*-DNA PCR on skin biopsy of EI lesions,[9] but a few investigators have not found PCR to be a useful test in cutaneous TB.[13] We believe that the recent molecular biology evidence that *M. tuberculosis* DNA is present in a majority of EI lesions together with the successful response to anti-TB therapy supports the hypothesis that most cases of EI are due to a paucibacillary *M. tuberculosis*-DNA infection of the skin.

We recommend that EI patients be given a trial of anti-TB therapy (for example, isoniazid 300 mg by mouth once daily, rifampicin 600 mg by mouth once daily, pyrazinamide 1.5 g. by mouth once daily, and ethambutol 800 mg by mouth once daily for the first 2 months, then continue isoniazid and rifampicin for another 4 months) while waiting for *M. tuberculosis*-DNA PCR results, or evaluating the response to therapy in 4 weeks.

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what's your diagnosis?

A 40-year old obese female with altered sensorium

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A 40-year old obese female was admitted with altered sensorium, a history of vomiting and documented hyponatremia followed by fluctuating encephalopathy and a deep coma state. She was initially managed at a peripheral health center where her serum sodium was 98 mEq/L. She was treated for severe hyponatremia (duration of hyponatremia and rate of correction not known) with a slight improvement noticed by her family members initially. The patient was managed inititally at a primary health center by a primary care physician with slight improvement but soon developed fluctuating encephalopathy and was shifted to our medical center. On admission, the patient was still in a stuperous state with spontaneous guttural vocalization only and no active movement of her limbs. On examination, the patient had asymmetrical extrapyramidal signs–more on the right side compared to the left. The patient had normal pupillary reflexes and maintained ocular movements. Spastic paralysis of all four limbs was associated with brisk deep tendon reflexes, hypertonia and the Babinski sign (the patient was in a locked-in like state with maintained ocular movements, normal pupillary reaction, brisk deep tendon reflexes and flexor responses to planters). The rest of the systemic examination was normal.

Routine tests were normal except for serum sodium of 115 mEq/L and serum potassium of 1.98 mEq/L. The patient underwent magnetic resonance imaging (MRI) of the brain (Figure 1a).

1. What are the findings on the MRI scan of the brain?
2. What is the likely diagnosis in this clinical setting?

Answer on page: 308

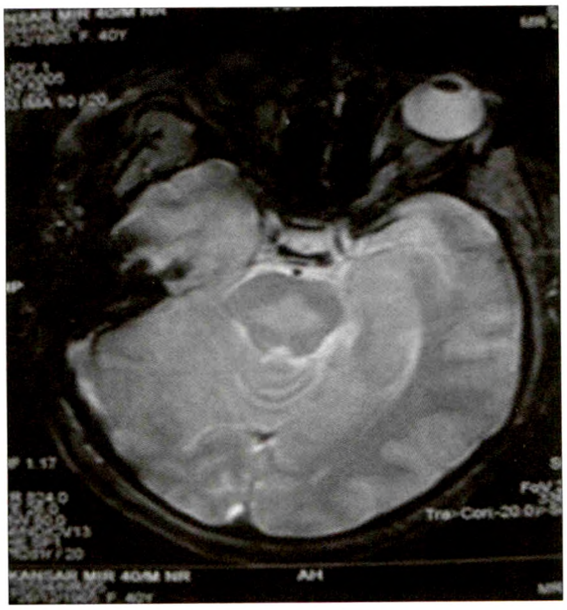

Figure 1a. A trident-shaped area of T2 hyperintensity (arrow) in the central pontine region in the axial plane on cranial MRI scan.

PubMed-indexed duplicate publications in the last decade, 1996-2006

To the Editor: I have read with great interest the recently published editorial on the policy of your prestigious journal concerning duplicate publication.[1] It motivated me to perform an analysis of the PubMed-indexed publications from the last decade that were assigned the NLM Publication Type "Duplicate publication [PT]", aiming to clarify to the readers and authors some of what they should know about duplicate publication. A search strategy was undertaken including "Duplicate publication [PT]" directed to PubMed within a single hour limit (on April, 25th, 2007), limited to citations "published in the last 10 years" from the aforementioned date. The number of all PubMed-listed biomedical studies published in the last decade totaled 5 553 528 citations, of them 30 744 belonged to authors affiliated to Arab institutions (0.55%). Of the total 5 553 528 citations, 382 were of the "duplicate publication" type. The Medline format of the text file was then converted, using a locally designed visual basic program into a Microsoft Excel file, which eventually was captured as a new database query via SPSS software ending with 382 records in SPSS data file format. Because the search of duplicate publications in PubMed returns almost the double its actual number by showing both the original and the duplicate, the author read thoroughly all the abstracts of the 382 articles and looked meticulously into its contents. Moreover, the author sorted the fields of title and first author name in the data file to detect resemblance in the titles and authors' names in all studies. However, some duplicate publications have different but near titles and a few have the same first author but a different number of coauthors. Finally, the actual number of duplicate publication was only 226 articles (0.004%) without any duplication in the SPSS data file. The reason behind exceeding the half could be explained by many factors. Some of articles appeared only as a single duplicate publication in PubMed because it was earlier and originally published in a non-indexed journal and then in the indexed one.[2] Also, there could be some delay or reluctance in notifying PubMed. Some of the 2006 duplicate publications might only show in 2007, which was not included in the search. Table 1 shows that the number of duplicate publications increased during the years 2002-2007 than in the first five years of the last decade. There was no significant change in the percentage of research on human subjects, articles in English, nor the place of journal of publication between the first and second five years of the last decade. There was a nonsignificant trend of increase in author number and also a nonsignificant decrease in the percentage of review, clinical trials and editorial articles of duplicate publication between the two groups of years. Only two articles from the total of 226 were retracted and two studies –one of them was retracted-were authored by a researcher affiliated to Arab institutions.

Duplicate publication is considered a type of self-plagiarism along with data fragmentation (i.e., salami-slicing), copyright infringement, and the practice of text recycling.[3] Plagiarism is taking over ideas or words of another without acknowledging him or her. Using one's own written product in a new article without letting the reader to know the original source of the first product is self plagiarism.[3] Duplicate publications occur because of the pressure to publish in a culture of "Publish or Perish", not understanding the seriousness and how duplicate publication could distort data aggregation in systemic reviews, the reluctance of academic leaders or journals to condemn the practice, or punish cases, not doing enough by journals to publish clear definitions and/or identify cases during peer review process.[4] The length of peer review time and the uncertainty of accepting research for publication felt by authors could also be added to the aforementioned causes. Although the percentage of duplicate publications from the total (0.004%) in the last decade was very small, it does not give the true picture of the problem, especially for the Arab world where authors mostly publish in non-indexed journals. Mojan-Azzi et al[5] developed an electronic search engine for redundancies to estimate the amount of duplicate publication in scientific journals. They applied their method to 22 433 articles published between 1997 and 2000 in 70 Medline-indexed ophthalmologic journals. Albeit they estimated that 1.39% of the publications were redundant, they regarded their estimate as the "tip of the iceberg".[5]

Because "no uniform standards and procedures for investigating duplicate publications are available", journal editors, suspecting duplicate publication, should work together, and invite independent reviewers to make the decision of duplicate publication.[6] Journals could also "require that authors sign statement denying or disclosing overlapping" in their manuscripts, and "arrange with other journals to impose sanctions on authors of redundant articles".[4] Moreover, there is a need to register planned and ongoing clinical trials and to change emphasis from quantity to quality by requiring applicants of post and grants.[5]

Table 1. Comparison of PubMed indexed articles of duplicate publication type in the last decade 1997-2006 (n=226).

Characteristics of duplicate publications		1997-2001(n=83)	2002-2006(n=143)	Total	Tests of significance, *P*
Number of authors (in 9 articles no author was mentioned)					
Single author	N	17	19	36	
	%	21.79	13.67	16.59	
4-5 authors	N	40	82	122	
	%	51.28	58.99	56.22	
5 or more	N	21	38	59	
	%	26.92	27.34	27.19	χ^2=2.46, 0.29
Mean number of authors	Mean	4.26	4.45	4.15	F=0.4, 0.527
Clinical study (Human subjects)	N	70	106	176	
	%	84.34	74.13	77.88	χ^2=3.3, 0.096
Article in English	N	69	122	191	
	%	83.13	85.31	84.51	χ^2=0.19, 0.71
Type of publication					
Journal article	N	37	77	114	
	%	44.58	53.85	50.44	
Review	N	12	13	25	
	%	14.46	9.09	11.06	
Clinical trial	N	7	10	17	
	%	8.43	6.99	7.52	
Editorial	N	3	3	6	
	%	3.61	2.10	2.65	
Others	N	24	40	64	
	%	28.92	27.97	28.32	χ^2=2.83, 0.59
Place of journal publication					
USA	N	35	63	98	
	%	42.17	44.06	43.36	
Elsewhere	N	48	80	128	
	%	57.83	55.94	56.64	χ^2=0.08, 0.89
Authors affiliated to Arab institutions	N	1	1	2	
	%	1.2	0.7	0.9	Fisher exact not significant, *P*=1
Retracted publication					
	N	1	1	2	
	%	1.2	0.7	0.9	Fisher exact not significant, *P*=1

Responding to duplicate publications, journals should notify authors and impose restrictions on their future submission, inform authors' institutions and funding sources of the research, publish notices for the readers, and inform other journals and indexing services.[4] Only in severe cases, is duplicate publication retracted,[6] which is consistent with what the current study data shows of retraction of duplicate publications in only 0.5% of the cases.

Von Elm et al[7] analyzed articles in systematic reviews in anesthesia and analgesia, 1989-2002, to investigate patterns of duplication and propose a decision tree for classification. They identified different patterns of duplications and found that of the duplicates, 64% had partly or completely different authors from the main article. Hence they concluded that authorship was an unreliable criteria of duplication.[7] Therefore, the decision of banning the co-authors from submitting manuscripts to the *Annals of Saudi Medicine* would not be questionable only if it came after ensuring the similarity of the list of authors on the byline for both the main and duplicate articles. It could be difficult, especially when some of the regional journals still do not require all authors on the byline to sign an assignment of copyright. Moreover, some regional journals do not require assignment of copyright at all. The shared responsibility of all authors for their article is undeniable. However, there could be some odds of the innocence of a part of the co-authors. Then, the first or the corresponding author should take the responsibility of his misconduct. In the Poehlman case of data falsification,[8] Poehlman[9] took the sole responsibility for the falsification, and publicly exonerated his coauthors in his letter of apology.[9]

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Reply

Dear Dr. Afifi: Thank you for raising an important issue and providing the data on duplicate publication in the region. In response to your comment about our policy, our decision to ban all authors on manuscripts submitted to the Annals that are found to have been previously published is based on an assumption that all authors partook in the study and were aware of the original publication and the second submission. If they later convince us that their names were placed on the new submission without their knowledge, we may remove them from the banned list. As you say, they could be innocent. In searching for possible previous publication, we rely initially more on the title and abstract than on author names. When different authors appear on the new submission compared with the original publication this suggests that new authors were not involved in the study reported in the first published version of the manuscript, raising the issue of contributorship in addition to duplicate submission. Presumably their contribution to the study was not sufficient to warrant inclusion in the original list of authors. We have to assume that all authors on the new, duplicate submission were at least aware of the previous publication, unless they convince us otherwise.

John T. Cathey
Senior Editor
Mahmoud Aljurf, MD
Editor-in-Chief

Arab and Muslim Physicians and Scholars

Abu Bakr Muhammad Ibn Zakariya Al Razi (Rhazes): Philosopher, Physician and Alchemist

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Ann Saudi Med 2007; 27(4): 305-307

Abu Bakr Muhammad Ibn Zakariya Al Razi was born in Al Rayy, a town on the southern slopes of El Burz mountains near present-day Tehran, Iran, in the year 865 AD (251 Hegira). His early interests were in music. He then started studying alchemy and philosophy.[1] At the age of thirty, he stopped his work and experiments in alchemy due to eye irritation by chemical compounds he was exposed to. Among his discoveries in alchemy, he is credited with the discovery of sulfuric acid and ethanol.

His teacher in medicine was Ali Ibn Sahl Rabban al-Tabari, a physician and philosopher born to a Jewish family in Merv, Tabaristan of modern-today Iran. Ibn Rabban converted to Islam during the rule of the Abbasid Caliph Al-Mu'tasim who took him into the service of the court, in which he continued under the Caliph Al-Mutawakkil. Al-Razi studied medicine and probably also philosophy with Ibn Rabban. Therefore, his interest in spiritual philosophy can be traced to this master. Al Razi quickly surpassed his teacher, and became a famous physician. He was appointed as director of the hospital of his hometown Al Rayy during the reign of Mansur Ibn Ishaq Ibn Ahmad Ibn Asad of the Samanian dynasty. Al Razi's fame reached to the capital of the Abbasids. He was called upon by Caliph Al Muktafi to be the chief director of the largest hospital in Baghdad. Al Razi is attributed with a remarkable method for selecting the site of a new hospital. When the Chief Minister of Al Muktafi, named Adhud Al Daullah, requested him to build a new hospital, he had pieces of fresh meat placed in various areas of Baghdad. A few days later, he checked the pieces, and he selected the area where the least rotten piece was found, stating that the "air" was cleaner and healthier there.

Following the death of Caliph Al-Muktafi in 907, Al Razi returned to his hometown Al Rayy. He was in charge of the hospital there and dedicated most of his time for teaching. It is said that he had several circles of students around him. When a patient came with a complaint or someone from the laity had a question; it was passed to the students of the "first circle". If they could not give an answer, then it was passed to those in the "second circle" and so on. If all failed to give an answer, then it came to Al Razi who gave the final answer.

Al Razi was quite generous and charitable for his patients, treating them in a quite humane manner, giving them treatment without charging them. In his latter years, he had cataract in both eyes and became blind. He died in Al Rayy on October 27, 925 at the age of 60 years.

He wrote more than 224 books on various subjects. His most important work is the medical encyclopedia known as *Al-Hawi fi al-Tibb*, known in Europe as *Liber Continens*. His books in medicine, philosophy and alchemy had greatly effected the human civilization, especially in Europe.[1] Some authors considered him the greatest Arabic-Islamic physician and one of the most famous known to humanity.[2]

Richter-Bernburg wrote a comprehensive bio-bibliographical survey of Al Razi's medical works which had a great impact on posterity, and illustrated the textual scholarship and clinical observations of this greatest medical practitioner and writer.[3] His most significant books were:

1. *Kitab Al-Hawi (Liber Continens)*, a compilation of his readings of Greek and Roman medicine, his own clinical observations and case studies, and methods of treatment during his years of medical practice. It is generally thought that this book was compiled by his students after his death. It was translated in 1279 to Latin by Faraj Ibn Salim, a scholar working at the Court of the king of Sicily. The first Latin edition of the "*Continens*", published at Brescia, Italy, in 1486, is the largest and heaviest book printed before 1501.

This book was considered the most significant medical book in the medieval ages. The fame of Al Razi as one of the greatest Muslim physicians is mainly due to the case records and histories written in this book.

2. *Kitab Al Mansuri Fi al-Tibb (Liber Medicinalis ad Almansorem)* is a concise handbook of medical science that he wrote for the ruler of Al Rayy Abu Salih Al-Mansur Ibn Ishaq, the ruler of Al Rayy around the year 903.

3. *Kitab Man la Yahduruhu Al-Tabib (Book of Who is not Attended by a Physician or A medical Advisor for the General Public)* is dedicated to the poor, the traveler, and the ordinary citizen who could consult or refer to it for treatment of common ailments when a doctor was not available.

4. *Kitab Būr' al-Sā'ah (Cure in an Hour)* is a short essay by Al-Razi concerning ailments that he claims can be cured within an hour's time. They include headache, toothache, earache, colic, itching, loss of feeling in numb extremities, and aching muscles.

5. *Kitab al-Tibb ar-Ruhani (Book of Spiritual Medicine).*

6. *Kitab al-Judari wa al-Hasbah (The Book of Smallpox and Measles).*

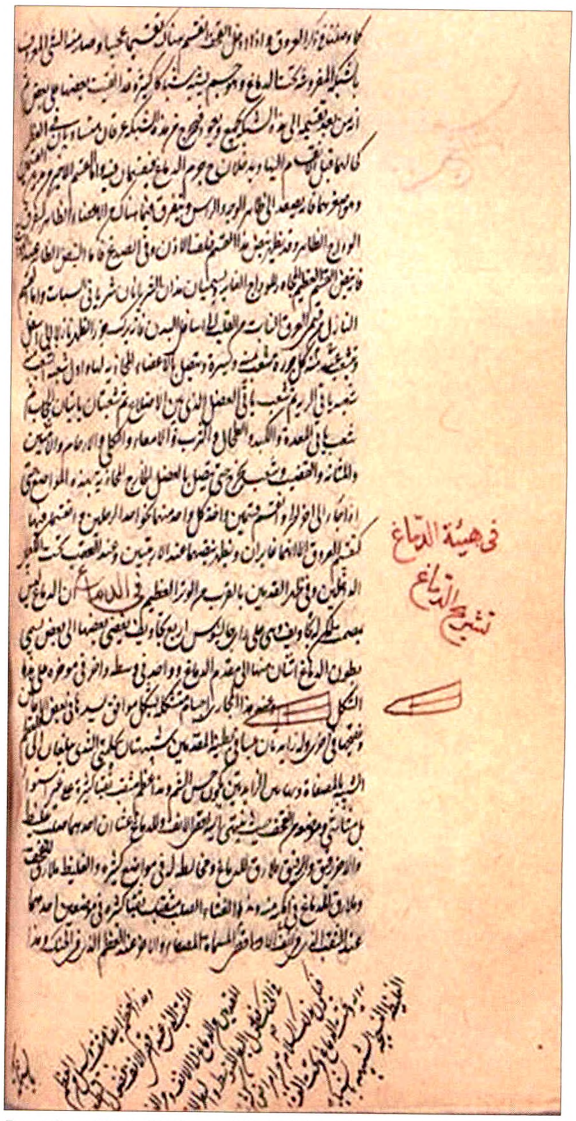
7. *Kitab al-Murshid (The Guide)* is a short introduction to basic medical principles that were intended as a lecture to students.

8. *Al Shakook ala Jalinoos, (The Doubt on Galen).* In this book he criticized some of Galen's theories, particularly the four separate "humors" (liquid substances, including blood, phlegm, yellow bile and dark bile), whose balance were thought to be the key to health and a natural body-temperature. He reported that Galen's descriptions did not agree with his own clinical observations.

9. *Al Syrah al-Falsafiah (The Philosophical Approach).*

10. *Kitab Sirr Al-Asrar (Book of Secret of Secrets)* deals with alchemy.

Al Razi utilized case histories extensively in his writing as an educational tool and as documentation of the various illnesses he diagnosed and treated. Alvarez-Millan discussed the description of diseases occurring in *Kitab al-Tajārib*, the largest and oldest collection of case histories, so far as is known, in medieval Islamic medical literature. Since Al Razi was a prolific medical writer, that discussion includes a review of his medical and therapeutic principles dealing with eye diseases, as described in his learned treatises, and a comparison with those therapies actually employed in his everyday practice.[4] Rhazes made important contributions to neurology and neuroanatomy. He stated that nerves had motor or sensory functions, describing 7 cranial and 31 spinal cord nerves. He assigned a numerical order to the cranial nerves from the optic to the hypoglossal nerves. He classified the spinal nerves into 8 cervical, 12 thoracic, 5 lumbar, 3 sacral, and 3 coccygeal nerves. In his clinical case reports cited in his books *Kitab al-Hawi* and *Al-Mansuri Fi At-Tibb*, he showed an outstanding clinical ability to localize lesions, prognosticate, and describe therapeutic options and reported clinical observations, emphasizing the link between the anatomic location of a lesion and the clinical signs. Al Razi was a pioneer in applied neuroanatomy. He combined a knowledge of cranial and spinal cord nerve anatomy with an insight-


في هيئة الدماغ
تشريح الدماغ

Page from Kitab Al Mansuri fi al Tibb on the morphology and anatomy of the brain (National Library of Medicine). The text in red reads: On morphology of the brain: Anatomy of the brain. The page describes in amazing detail the ventricles of the brain, as well as other observations.

ful use of clinical information to localize lesions in the nervous system.[5] In addition, he is credited as the first physician to clearly separate and recognize concussion from other similar neurological conditions.[6]

In addition to his contributions to the neurological sciences, he was a pioneer in the treatment of mental illnesses. When he was the director of the main hospital in Baghdad, he established a special section for the treatment of the mentally ill. He treated his patients with respect, care, and empathy. As part of discharge planning, each patient was given a sum of money to help with immediate needs. This was the first recorded reference to psychiatric aftercare.[7]

Al Razi is considered the "original portrayer" of smallpox.[8] While serving as the Chief Physician in Baghdad, he was the first to describe smallpox and to differentiate it from measles. He wrote a treatise on the subject: "Kitab al Judari wa al Hasbah". This book was translated more than dozen times into Latin. In spite of this, it is of interest to know that European physicians continued to confuse these two illnesses until recently.[9]

The first monograph written on pediatrics was authored by Al Razi. It is known in Latin as *Practica Puerorum*. Radbill reviewed a Latin translation of this treatise, which is labeled a "Booklet on the Ailments of Children and their Care".[10] The book has 24 chapters dealing with various illnesses in newborns, infants and children. The topics covered included skin diseases, eye and ear diseases, and gastrointestinal symptoms such as vomiting, abdominal distention, diarrhea and constipation. He devoted chapters to paralysis, epilepsy and enlargement of the head (hydrocephalus).

Al Razi advocated the use of honey as a simple drug and as one of the essential substances included in composed medicines.[11] His contributions to pharmacology include the introduction of mercurial ointments. He developed instruments used in apothecaries (pharmacies) such as mortars and pestles, flasks, spatulas, beakers and glass vessels.

There is much more to be discussed about the contributions of this great Muslim scholar to philosophy, chemistry and medicine. We can not give him justice in a short article. The more we learn about his contributions and life dedicated to medicine, the more we value our Islamic cultural and scientific heritage.

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what's your diagnosis?

Diagnosis: Osmotic myelinolysis (central pontine myelinolysis and extrapontine myelinolysis)

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Osmotic myelinolysis (OM) is an acute, non-inflammatory demyelinating disease that can develop following rapid correction of hyponatremia from any cause. Adams and colleagues[1] originally described it in 1959, using the term central pontine myelinolysis, as a unique clinical entity affecting alcoholics and the malnourished. Since 1962, lesions outside the pons (extrapontine) were increasingly recognized, so the term "osmotic myelinolysis" seems to be more appropriate. In 1950, Adams and Victor observed a rapidly evolving quadriplegia and pseudobulbar palsy in a young alcoholic man whose postmortem examination disclosed a large, symmetrical, essentially demyelinative lesion occupying the greater part of the base of the pons. In 1959, Adams et al reported four more cases using the term central pontine myelinolysis.

The outstanding clinical characteristic of OM is invariably associated with other serious, often life threatening disease. In more than half the cases, it has appeared in the late stages of chronic alcoholism, often in association with Wernicke disease and polyneuropathy. Among other medical conditions and diseases with which OM has been conjoined are a malnourished status, chronic renal failure being treated with dialysis, diabetes mellitus, hepatic failure and post-orthotopic liver transplantation,[2] advanced lymphoma, carcinoma, severe bacterial infections, dehydration and electrolyte disturbances, acute hemorrhagic pancreatitis, and pellagra. It can also occur in healthy persons with hyponatremia caused by gastroenteritis or diuretic therapy. There are many reports of the disease in children, particularly in those with severe burns.[3] Osmotic myelinolysis following treatment of hyponatremic dehydration is reported even during infancy.[4] Young children and adults of all ages and both sexes can be affected. OM occurs sporadically, with no hint of a genetic factor.

The pathogenesis of myelinolysis, and the reasons for vulnerability and predilection of particular brain territories to develop myelinolysis are not fully understood. Pathologically, the fundamental abnormality consists of destruction of the myelinated sheaths throughout the lesion, with relative sparing of the axons and intactness of the nerve cells. Signs of inflammation are conspicuously absent. In contrast this pattern of damage is opposite to that of infarction and the inflammatory demyelinations of multiple sclerosis and postinfectious encephalomyelitis. Classically, the central basis pontis is involved, hence the original name of central pontine myelinolysis (CPM). Very rarely, the lesion may encroach on the midbrain, but only very rarely does it extend down to the medulla. Exceptionally, the extensive pontine lesions may be associated with identical myelinolytic foci symmetrically distributed in the thalamus, subthalamic nucleus, striatum, internal capsule, corpus callosum, amygdaloid nuclei, lateral geniculate body, white matter of the cerebellar folia, and deep layers of the cerebral cortex and subjacent white matter. The latter condition is termed extrapontine myelinolysis (EM).

Clinical reviews and experimental animal models have shown that the main contributing factor for the development of myelinolysis is the correction of hyponatremia, first suggested by Tomlinson in 1976 and subsequently proved convincingly by Laureno in his work on dogs and by Kleinschmidt-DeMasters and Norenberg on rats.[6] OM is especially likely to occur following rapid correction of hyponatremia (e.g., more than 12 mmol/L a day) and if the hyponatremia is chronic rather than acute prior to correction. Nevertheless, OM can still occur even after cautious and slow correction, especially in the presence of other recognized risk factors such as hypokalemia, liver or renal disease, and poor nutritional status. Hypokalemia, especially, has been reported as a possible trigger. About 90% of the cases reviewed by Lohr in 1994 were found to be hypokalemic[7] (as was

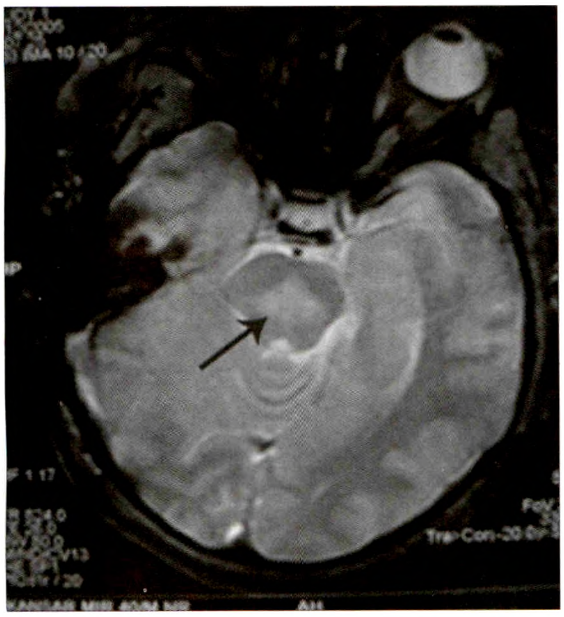

Figure 1a. Shows a trident-shaped area of T2 hyperintensity (arrow) in the central pontine region in the axial plane on cranial MR scan.

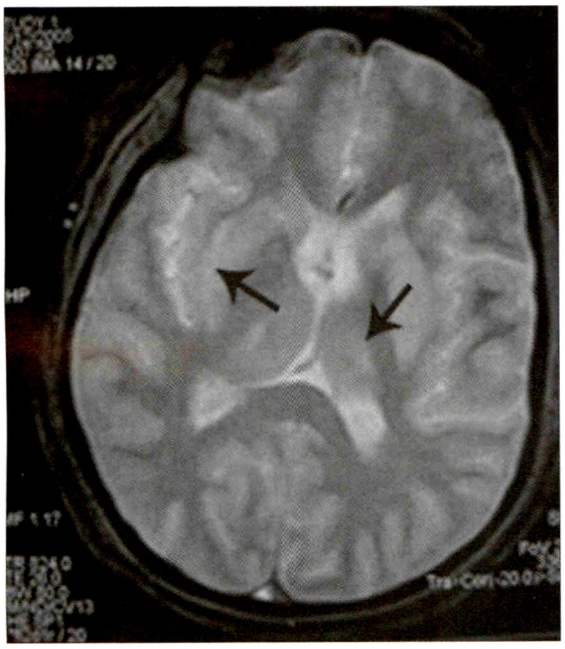

Figure 1b. Shows multiple areas of T2 hyperintensities in the basal ganglia and deep white matter (arrows), representing part of the same process as Figure 1a.

our patient). It is impossible to define a level of correction that will be absolutely free of risk. On the other hand, untreated hyponatremia, regardless of its severity, will not result in myelinolysis. In reference to the above, our patient had an initial serum sodium of 98 mEq/L and serum potassium of 1.98 mEq/L at the time of presentation. Serum sodium and potassium were corrected over a period of time to normal levels but the patient developed progressive neurological deterioration. MRI of the brain later revealed typical features as described above.

The clinical course of affected patients may be biphasic. Following clinical improvement from hyponatremic encephalopathy, a neurologic syndrome caused by myelinolysis typically ensues 2-3 days after the correction of hyponatremia. Initial symptoms include mutism, dysarthria, lethargy and affective changes. Later, the classical symptoms of spastic quadriparesis and pseudobulbar palsy develop, reflecting damage to the corticospinal and corticobulbar tracts in the basis pontis. These symptoms may develop in more than 90% of patients. A large central pontine OM can cause a locked-in syndrome. Extrapontine involvement can present with varying movement disorders such as ataxia, dystonia and Parkinsonism.

Radiologically, OM manifests as regions of increased water content. Although CT scans of patients with clinically apparent CPM may show central pontine radiolucency, MRI is much more sensitive and the imaging method of choice for the diagnosis. The MRI discloses a characteristic "bat wing" lesion of the basis pontis in typical cases (Figure 1a and 1c). Lesions appear as hypointense in T1-weighted and hyperintense on T2-weighted acquisitions and are non-contrast enhancing. Enhancement following intravenous gadolinium-DTPA injection is rare though it has been reported. Imaging findings may not be apparent within the first 2 weeks of illness in some cases. For these reasons, a diagnosis of OM should not be ruled out simply on the basis of negative CT/MRI scans. There is also no correlation between the size of the lesions on imaging and the clinical severity of the neurological manifestations. The regions affected are also characteristic: CPM affects the basal pons with sparing of the descending corticospinal tracts as well as peripheral pontine tissue. The corticospinal tracts may appear as preserved islands within a zone of hyperintense pontine demyelination on T2-weighted MRI images. There may be a significant delay in the appearance of lesions on MRI and hence a repeat study after 2 weeks may be needed in cases where diagnosis is likely. EPM typically involves the basal ganglia and the lateral thalamic nuclei (Figure 1b). In a review necropsy series by Gocht and Colmant of 58 cases of OM, 27 cases had CPM, 18 had both CPM and EPM while 13 cases presented as isolated EPM.[8]

The signal intensity changes of OM on MRI are non-specific. Various other disease processes may some-

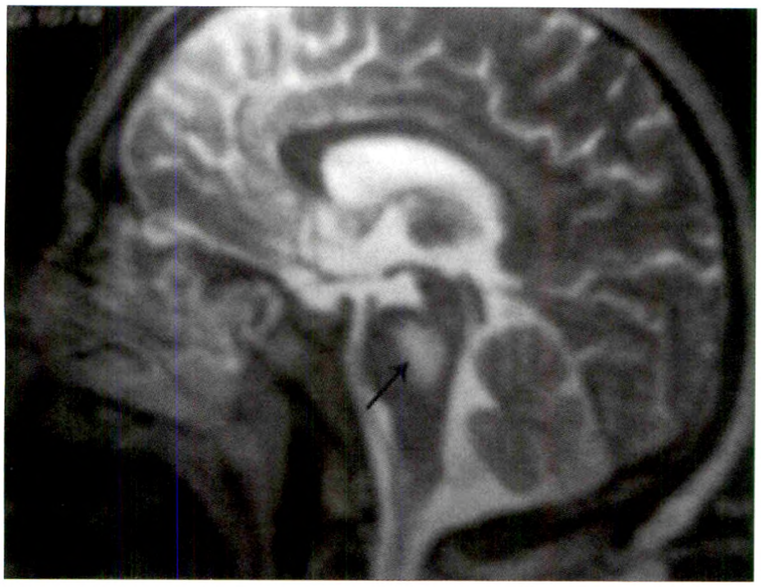

Figure 1c. Represents a midsagittal T2-weighted MRI image showing a triangular hyperintense lesion in the midpons (arrow).

what produce similar findings. Brainstem neoplasms such as glioma and metastasis may appear somewhat like OM, but usually present in a more subacute manner. Infarction, multiple sclerosis, encephalitis, and acute disseminated encephalomyelitis often show more diffuse involvement in the supratentorial regions, and therefore clinical differentiation is not problematic. Post-irradiation and post-chemotherapy changes can easily be diagnosed from the clinical history in most cases. Nevertheless, symmetrical involvement of the central pons on CT/MRI scans should suggest OM in the acute clinical setting, especially in the presence of recent sodium correction. Furthermore, concomitant involvement of the pons and basal ganglia is fairly specific of OM. Hypoxic encephalopathy, Leigh's disease and Wilson's disease are a few other differential considerations that can be excluded on clinical grounds.

Other diagnostic tests may be helpful in establishing the diagnosis of OM. Brainstem auditory evoked potential studies may identify pontine lesions early in the course of myelinolysis when imaging is normal. Routine CSF studies are usually normal, but CSF protein levels and myelin basic protein levels may be elevated in OM but not in hyponatremia. Electroencephalograms are non-specific and frequently show generalized slowing. Recently, 18-fluorodeoxyglucose positron emission tomography (PET) has been reported to show transient glucose hypermetabolism in the pontine lesions in the early stage of the disease, which later evolved into a hypometabolic state.[9]

Treatment of myelinolysis is essentially supportive. Therapeutic guidelines for correction of hyponatremia are still being considered. Karp and Laureno, on the basis of their experience and that of Sterns et al, have suggested that the hyponatremia be corrected by no more than 10 mEq/L in the initial 24 hours and by no more than about 21 mEq/L in the initial 48 hours. Medications can alleviate symptoms of myelinolysis such as depression, psychosis and abnormal somatic movements. The myelinolysis itself cannot be specifically treated once it develops. Recently, therapeutic plasmapharesis has been reported as a safe and effective method of improving the clinical outcome. Although OM was once believed to be fatal with a survival rate of only 5% to 10% beyond 6 months, it is now clear that many patients survive much longer. The clinical outcome varies widely, and recovery can be complete or partial. Recommendations for management of hyponatremia stress the importance of slow correction; not more than 10 mEq/L in the initial 24 hours and by no more than about 21 mEq/L in the initial 48 hours.[10,11] Once it develops, myelinolysis itself cannot be treated but symptoms of depression, psychosis and abnormal somatic movements can be alleviated with medication. The clinical outcome varies widely, and recovery can be complete or partial.

In conclusion, OM (CPM and EPM) is a distinct entity with a unique clinical presentation resulting from aggressive treatment of chronic severe hyponatremia, with a possible contribution from associated hypokalemia as well. Physicians should be aware of this entity when dealing with hyponatremic patients. Management involves weighing the risk of the illness and possible death from untreated hyponatremia against the risk of developing OM. Obviously the duration of hyponatremia and the severity of related symptoms should be taken into consideration. Although radiological findings of OM are not specific, MRI is the radiological modality of choice in investigating suspected OM, and it is usually, but not exclusively, positive, within 2 weeks of onset of symptoms. Resolution of MRI findings appears to follow clinical improvement but bears no constant relationship. Ultimately the clinical picture remains the best guide to the patient's prognosis. An individual prognosis is difficult due to varied clinical outcomes including death, disability or complete recovery.

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errata

Vol 27;1 (January/February 2007): On page 37, Figure 2 was labeled as an MRI scan. It should have been labeled as a CT scan of hydatid cysts in the right paravertebral region.

Vol 26;5 (September/October 2006): On page 398, one of the author's names was misspelled. The correct spelling is Hatem A. Khalaf, not Khalef.

Vol 20;1 (January 2000): On page 83, one of the author's names was misspelled. The correct spelling is Ahmed Bahammam, not Bahamman.

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إعطاء ميثيلبريدنيسولون أو بوبيفاكين فوق الجافية أثناء العملية لتسكين الألم بعد جراحة استئصال قرص قطني: دراسة عشوائية باستعمال دواء غفل

المقدمة: يعاني كثير من المرضى الذين جرى لهم جراحة استئصال قرص قطني من ألم ظهري وجذري بعد العملية. مما يؤخر خروجهم من المستشفى واستئنافهم نشاطهم الطبيعي. يستعمل بعض الجراحين أثناء العملية تطبيق الستيرويدات القشرية فوق الجافية مع مخدر موضعي لتخفيف الألم بعد جراحة القرص القطني المفتوق. غير انه ما زالت هناك خلافات حول جدوى هذه العقاقير. الهدف من الدراسة الحالية هو مقارنة تأثيرات إعطاء ميثيلبريدنيسولون و بوبيفاكين فوق الجافية أثناء العملية مع تأثيرات إعطاء محلول ملحي عياري (دواء غفل) أثناء جراحة استئصال قرص قطني بالنسبة للسيطرة على الألم بعد العملية.

المرضى والطريقة: تم تقسيم مائة وخمسين مريضا. يعانون من انفتاق النواة اللبية على مستوى واحد (ق٤ - ق٥ أو ق٥ —ع١) لم تستجب لستة أسابيع من العلاج المحافظ ، إلى ثلاث مجموعات بصفة عشوائية. أجري لجميع المرضى عملية استئصال نصفي جزئي للصفيحة الفقرية واستئصال القرص. وفي نهاية العملية. وقبل إغلاق اللفافة. تم التقطير فوق الجافية والجذر العصبي المكشوف ٤٠ ملغم ميثيلبريدنيسولون مع ٣ مل محلول ملحي عياري للمجموعة رقم ١. و٢ مل بوبيفاكين ٥٪ مع ٢ مل محلول ملحي عياري للمجموعة رقم ٢. و٤ مل محلول ملحي عياري للمجموعة رقم ٣. أجري تقييم لشدة الألم الظهري والجذري بعد العملية باستخدام مقياس بصري لارقمي قبل العملية وبعد ٢٤ و٤٨ و٧٢ و٩٦ ساعة من العملية.

النتائج: لم يكن هناك فرق مهم في شدة الألم الظهري والجذري بين المجموعات الثلاث.

الاستنتاج: إن إعطاء ميثيلبريدنيسولون أو بوبيفاكين فوق الجافية أثناء العملية لا يؤدي إلى تخفيف الألم الظهري والجذري بعد العملية.

الوظائف الإدراكية للمصابين بالاضطراب ثنائي القطب إبان استقرار الحالة المزاجية

المقدمة: ركزت الدراسات الحديثة على طبيعة الخلل الوظيفي الإدراكي لمرضى الاضطراب ذو القطبين. كان الغرض من الدراسة الحالية هو التقصي عن الأداء الإدراكي لدى الأفراد المصابين بالاضطراب ثنائي القطب مقارنة بمشاركين أصحاء أثناء فترة مزاجية جيدة.

المرضى والطرق: تألفت العينة من ٢٧ مريضاً مصاباً بالاضطراب ثنائي القطب إبان استقرار المزاج و ٢١ مشاركاً . تم تقييم أداء الذاكرة البصرية واللفظية، والانتباه، والوظائف التنفيذية والوظائف النفسية لكل مشارك.

النتائج: أظهر المصابون بالاضطراب ثنائي القطب نقص إنتباه وخللاً وظيفياً تنفيذياً مهمين إضافة إلى أداء ضعيف في مهام الذاكرة البصرية واللفظية مقارنة بالمشاركين الآخرين. ترابطت مدة المرض وإجمالي عدد النوبات طوال الحياة والنوبات السابقة ذات المظاهر النفسية مع تدني الأداء في ناحية مهام الذاكرة والتنفيذ والانتباه. لم يكن الأداء النفسي مرتبطاً بالنقص الإدراكي.

الاستنتاج: أظهرت الدراسة الحالية ضعفاً إدراكياً باقياً في التحكم في التثبيط والانتباه الانتقائي وكذلك الأداء الضعيف في اختبارات الذاكرة البصرية واللفظية لدى مجموعة معتدلي المزاج المصابين بالاضطراب ذو القطبين. ترابط الأداء العصبي النفسي الضعيف مع استمرار المرض، وإجمالي عدد النوبات طوال الحياة والنوبات السابقة ذات المظاهر النفسية. يبدو أن الخلل الوظيفي المتعلق بالانتباه خاصية شاذة للعينة التي تمت دراستها.

نمط طاخات باب الشاذة في الدول النامية: تقرير من مستشفى حالات كبير بالمملكة العربية السعودية حول استخدام نظام يتسادا ٢٠٠١ المراجع

المقدمة: قليلة هي التقارير التي تصف تكرار أنماط شذوذات لطاخات باب وتواترها في الدول النامية باستخدام نظام بيتسادا المراجع الخاص باللطاخات. درسنا نمط الآفات داخل ظهارة عنق الرحم والأورام السرطانية التي يتم التقصي عنها بواسطة اللطاخات الخاصة بالإناث السعوديات في المنطقة الغربية بالمملكة العربية السعودية باستخدام نظام مراجعة.

المرضى والطرق: جرى إعادة تصنيف لجميع لطاخات عنق الرحم الواردة إلى قسم علم الأمراض بمدينة الملك عبد العزيز الطبية بجدة ابتداءً من ١ يناير ١٩٩٨م حتى ٣١ أغسطس ٢٠٠٥م وفقاً لنظام المراجعة مع تحديد مدى الأعمار.

النتائج: من بين ٥٥٩٠ عينة مقبولة تم تعريف ٢٦١ عينة (٥٪) كعينات شاذة ثم تم تصنيفها كخلايا وسفية لا نمطية ذات أهمية غير محددة (١٠٣ حالة، ٤٠٪)، وخلايا وسفية عالية الدرجة (٦ حالات،٢٪)، وآفات داخل الظهارية وسفية منخفضة الدرجة (٦٥ حالة ٢٢٪)، وآفات داخل الظهارية وسفية عالية الدرجة (٣١ حالة ١٢٪)، وشذوذات خلوية غدية (٣٠حالة، ١١٪)، وسرطان الخلية الوسفية منتشر (٢١ حالة، ٩٪). جاء معدل الخلايا الوسفية اللا نمطية ذات الأهمية غير المحددة على الآفات داخل الظهارية الوسفية عالية الدرجة ١,٩٪. بلغت حالات الأورام السرطانية الغدية المنتشرة ١٤ حالةً (٤٪) ضمن مدى عمري متشابه بالنسبة لسرطان الخلايا الوسفية.

الاستنتاج: بالرغم مما أظهرته هذه الدراسة قلة حدوث للإصابة بشذوذات الخلايا الظهارية العنقية ومدى عنقي أوسع مقارنة بالدراسات الأخرى المنشورة عالمياً، فقد شددت النتائج على الحاجة إلى وجود برنامج جيد التنظيم لتحري عنق الرحم مدعم بدراسات وطنية واسعة حول أنماط الشذوذات العنقية في البلاد. ستشجع المعلومات المتوفرة في هذه الدراسة على استخدام اللطاخات كطريقة فرز للتقصي عن سرطان عنق الرحم في الدول النامية.

الزرق الخلقي الأولي لدى الأطفال مترافقاً بموجودات شاذة على تصوير الدماغ بالمرنان

مقدمة: يظهر الزرق الخلقي في الشهور الخمسة الأولى من الحياة، وعملياً عند الولادة. يتسم الزرق الخلقي بتشوهات بسيطة في الزاوية القزحية القرنية للحجرة الأمامية للعين. تشمل الأعراض السريرية الدماع ورهاب الضوء وكبر المقلة، وهي تظهر في الشهر الأول. تلعب تقنيات التصوير مثل التصوير المقطعي البصري الترابطي وقياس سماكة القرنية دوراً هاماً في تقييم حالة الأطفال المشتبه في إصابتهم أو المصابين بالزرق. لم ترد نتائج تصوير الجهاز العصبي المركزي بالمرنان لدى المرضى المصابين بزرق خلقي أولي في الأدب الطبي. الهدف من هذه الدراسة هو استقصاء نتائج تصوير الدماغ بالمرنان لدى الأطفال المصابين بزرق خلقي أولي.

الطرق: قمنا بمراجعة الميزات الإشعاعية والباثولوجية والسريرية لدى الأطفال المصابين بالزرق الخلقي الأولي. تمت مراجعة ملفات ١٧ مريض بزرق خلقي أولي وكذلك تم تحليل صور الدماغ بالمرنان العائدة لهم.

النتائج: كانت نتائج التصوير بالمرنان غير طبيعية لدى ثلاثة مرضى ونقترح قصوراً في نمو الجسم الثفني. وكان لدى طفلين تأخر في تكون الميالين في الدماغ.

المناقشة: يقترح تكهف العصب البصري الشاذ والهام وزيادة قطر القرنية لدى مريضين مصابين بتأخر تكون الميالين أن الضغط داخل العين يمكن أن يكون أكثر شدة مما يظهر وجود علاقة قريبة بين الزرق الخلقي الأولي وشذوذ تكون الميالين في المادة البيضاء. يجب القيام بدراسة على المزيد من المرضى لتأكيد هذه النتائج.

انتشار حبوب اللقاح المؤرجة المحمولة في الهواء لنبات القطيفة الخضراء في سبع مناطق مختلفة في المملكة العربية السعودية

المقدمة: حبوب لقاح القطيفة الخضراء معروفة بأنها مؤرجة جدا، وسبب محتمل للأمراض الأرجية التنفسية. ومع ذلك، ما زالت البيانات المتوفرة حول انتشارها في البيئة محدودة أو غائبة عمليا في المملكة العربية السعودية.

الطرق: أجرينا استقصاء لتسجيل تعداد حبوب لقاح القطيفة الخضراء في الهواء وغيرها من حبوب اللقاح المؤرجة في الخبر والدمام وحائل وجدة وجيزان والقصيم والطائف باستخدام أجهزة العينات الحجمية بيركارد. تم تشغيل أجهزة العينات بصفة مستمرة لمدة سنة واحدة في كل موقع.

النتائج: أظهرت البيانات حبوب القطيفة الخضراء كأحد المكونات الرئيسية للأبواغ الهوائية في الهواء الطلق، إذ شكلت نسبة قصوى قدرها ٩٦٪ من التعداد الإجمالي لحبوب اللقاح في حائل، تليها الخبر (٨٩٪)، جدة (٨٧٪)، القصيم (٨٥٪)، الطائف (٨٤٪)، الدمام (٨٣٪)، جيزان (٦١٪). وقد ساهمت هذه النسب المئوية المرتفعة كثيرا في إجمالي حبوب لقاح النباتات الملتقطة خلال الفترة من أغسطس إلى نوفمبر في المناطق السبع كلها. وبالإضافة إلى ذلك أظهرت البيانات أن حبوب لقاح القطيفة الخضراء كانت موجودة طوال السنة مع اختلافات موسمية واضحة. أظهرت الدورية اليومية لخمسة مواقع على الأقل على مدى سنة نسبا قصوى من منتصف النهار إلى بداية المساء. وصل أقصى تركيز إلى ٣٠٠٠/م٣ من الهواء في أكتوبر و١٨٢٧/م٣ من الهواء في سبتمبر. كما أظهرت البيانات نمطا موسميا للنسب القصوى.

الاستنتاج: هناك حاجة لمزيد من الدراسات حول النواحي الكيميائية الحيوية والأرجية لتأكيد التأثير المؤرج لحبوب لقاح القطيفة والتحسيس في الأفراد الأرجيين في المملكة العربية السعودية.

معدلات حدوث السرطان بين السكان البحرينيين دراسة مدتها خمس سنوات (١٩٩٨م - ٢٠٠٢م)

الخلفية: السرطان هو السبب الثاني للوفيات ويأتي بعد أمراض القلب والأوعية، حيث تبلغ نسبته ١٢٪ من إجمالي الوفيات السنوية المبلغ عنها في البحرين. قمنا بتحديد الأنماط الوبائية للداء الخبيث في البحرين ومقارنتها مع تلك السائدة في أقطار مجلس التعاون الخليجي الأخرى والأقطار النامية الأخرى.

المرضى والطرق: تم الحصول على بيانات الدراسة من قاعدة بيانات سجل السرطان في البحرين. تم احتساب متوسط خمس سنوات لمعدلات الإصابة وأنواعها خلال ١٩٩٨م – ٢٠٠٢م باستخدام صيغة برامج (CANREG) تم استخدام معدلات الإصابة للعام ٢٠٠٠م لمقارنة البحرين مع الأقطار الأخرى في الخليج العربي باستخدام إحصاءات مركز الخليج لتسجيل السرطان.

النتائج: تم تسجيل ٢٤٠٥ حالة سرطان خلال فترة السنوات الخمس في البحرين (١٢٣٩ ذكراً و ١١٦٦ أنثى) مع متوسط سنوي ٤٨١ حالة. بلغت معدلات الإصابة العمرية العالمية القياسية ١٦٢,٣ و ١٤٥,٢ لكل ١٠٠٠٠٠ للبحرينيين الذكور والإناث على التوالي. على وجه العموم كانت هذه المعدلات مرتفعة لدى الذكور البحرينيين لمعظم أنواع السرطانات، وكان أكثر السرطانات شيوعاً هو سرطان الرئة للرجال (٣٥,٢ لكل ١٠٠٠٠٠) يأتي بعده سرطان المثانة (١٤,٥) والبروستات (١٤,٣) وسرطان الثدي للنساء (٤٦,٨) يأتي بعده سرطان الرئة (١٢,٢) والمبيض (٧,٧).

الخلاصة: بالمقارنة مع أقطار الخليج الأخرى، تعتبر معدلات الإصابة بالسرطان في البحرين مرتفعة بالنسبة لسرطانات الرئة والبروستات والقولون والمستقيم والمثانة والكلى والبنكرياس وابيضاض الدم بين الرجال وتنتشر سرطانات الثدي والرئة والمثانة والدرقية والرحم والمبيض بين النساء. من المحتمل تواصل اتجاه معدلات الإصابة بالسرطان نحو الارتفاع فيما يبدو لعدة سنوات أو حتى لعدة عقود قادمة.

المدونـــات الطبيـــة السعوديـــة

السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصّصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول مكتب المطبوعات (ر.إ ٣٦).

سعر الاشتراك ١٠٠ ريال في السنة للأفراد داخل المملكة و٢٠٠ ريال في السنة للأفراد خارج المملكة و٥٠٠ ريال في السنة للمؤسسات. يمكن فتح اشتراك مجاني للأفراد و المؤسسات في الدول النامية.

ترسل طلبات الاشتراك أو إلغاء الاشتراك الى البريد الإلكتروني: admin@saudiannals.com

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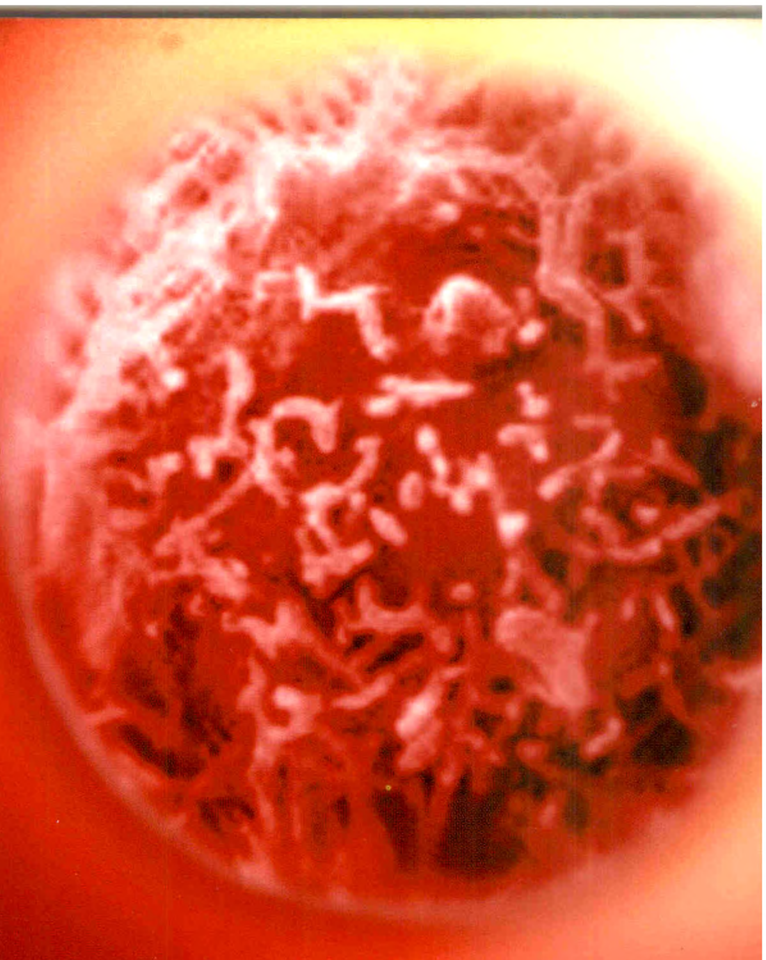

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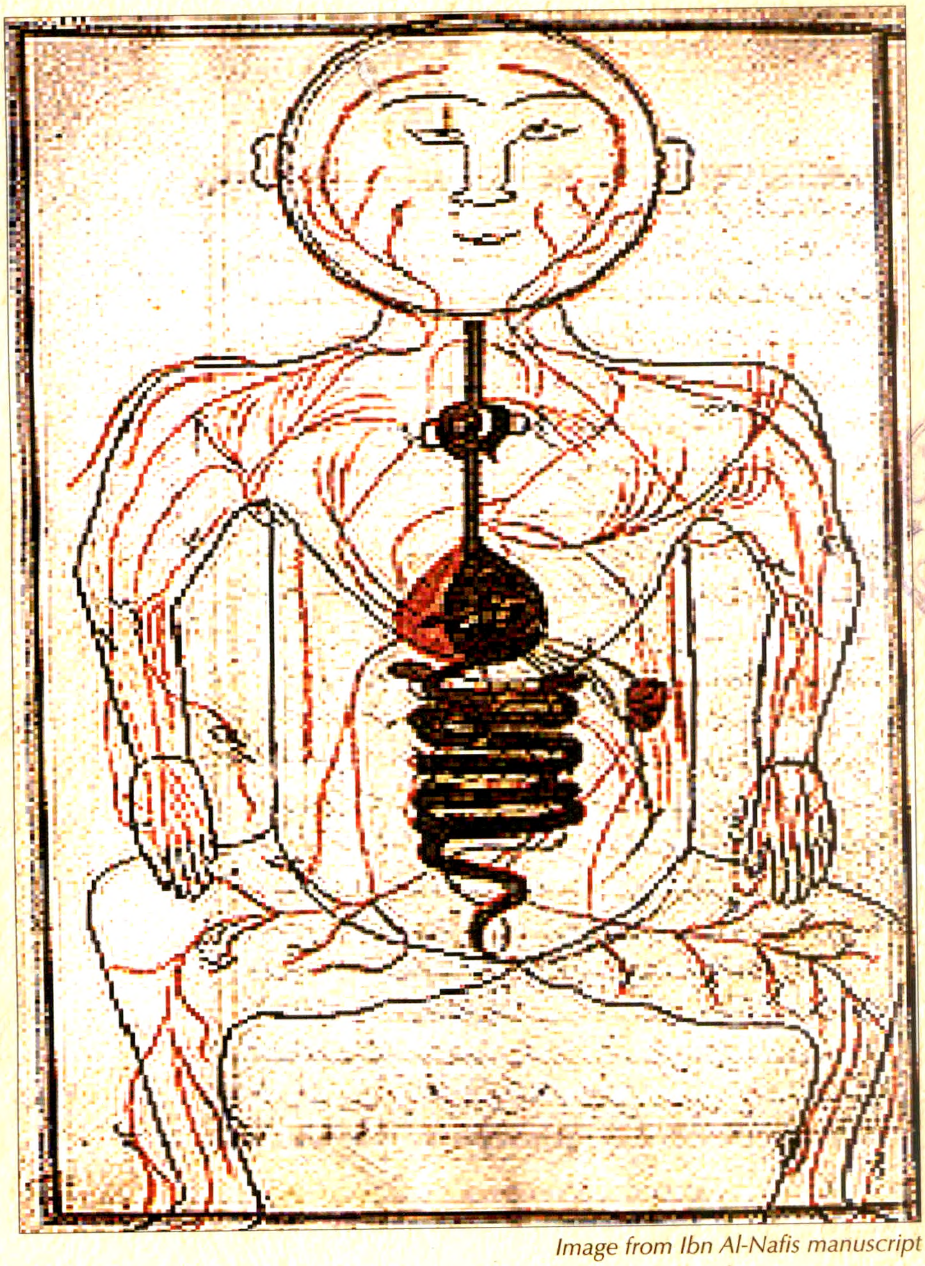

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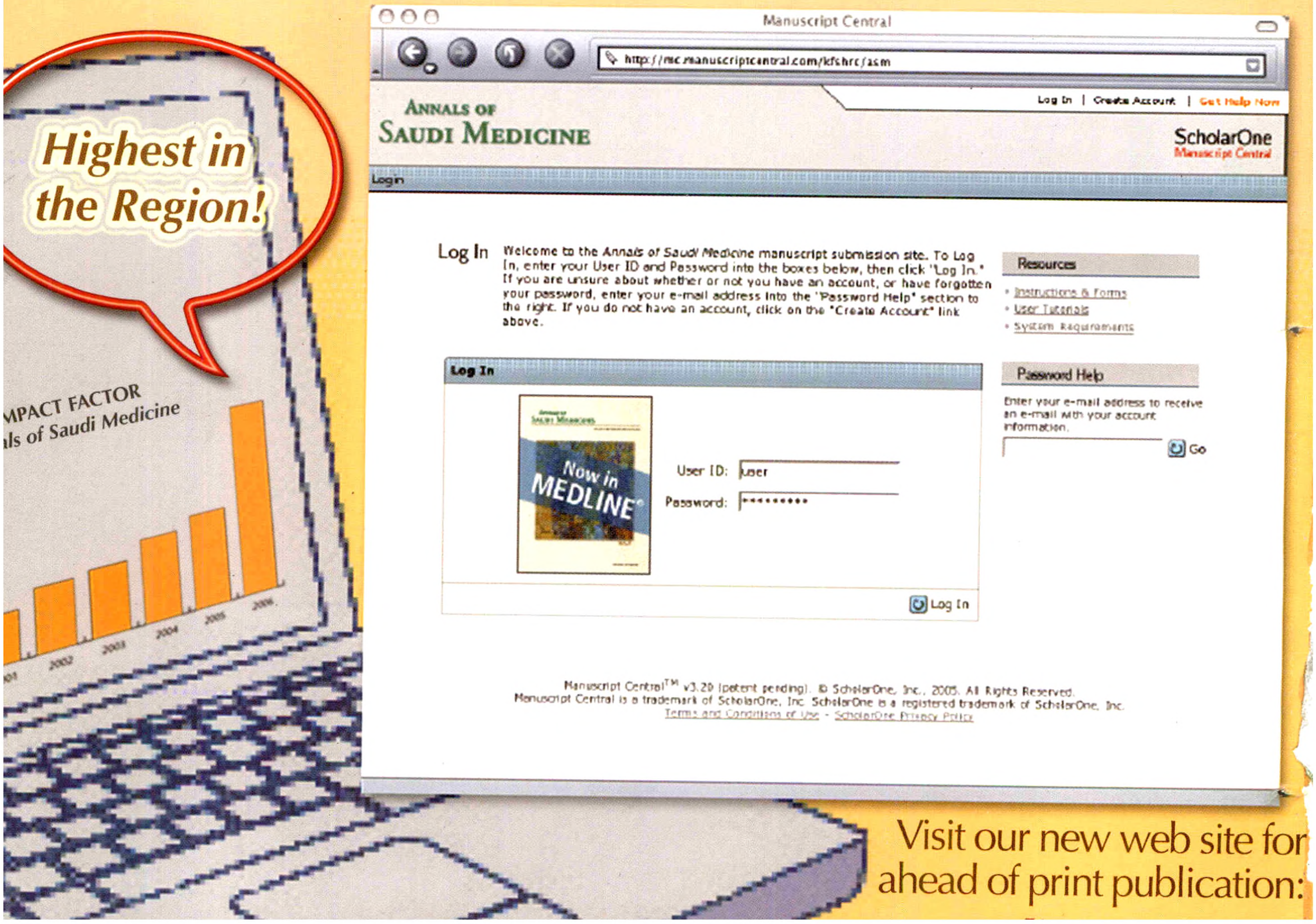

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03-04 April 2007/15–16 Rabia Al Awal 1428

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(Workshop by Dept.: 26 April 2007/09 Rabia Al Thani 1428)

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30 May 2007/13 Jumada Al Awal 1428

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للسعوديات فقط

إعــلان

يسر إدارة الإبتعاث والتدريب بالتعاون مع إدارة التمريض بمستشفى الملك فيصل التخصصي ومركز الأبحاث (مؤسسة عامة) أن تعلن عن رغبتها في إتاحة الفرصة للدراسة والتدريب في جامعة الملك سعود بن عبدا لعزيز للعلوم الصحية (كلية التمريض والعلوم الطبية المساعدة) للفتيات السعوديات والحصول على درجة البكالوريوس في علوم التمريض للفصل الدراسي القادم (**سبتمبر ٢٠٠٦**)

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- لايقل مجموع المواد العلمية واللغة الانجليزية عن ٨٥٪
- إجتياز الاختبار والمقابلة الشخصية المعد من قبل (**كلية التمريض والعلوم الطبية المساعدة**)
- تفرغ كامل للدراسة وان تكون لائقة جسدياً

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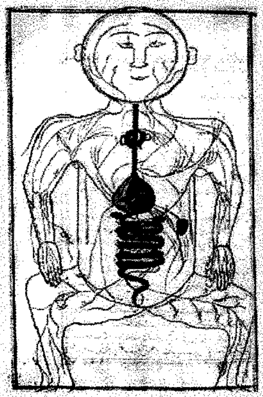

Image from the Ibn Al-Nafis manuscript, *Sharh al Qanun* showing the pulmonary blood circulation and digestive system.

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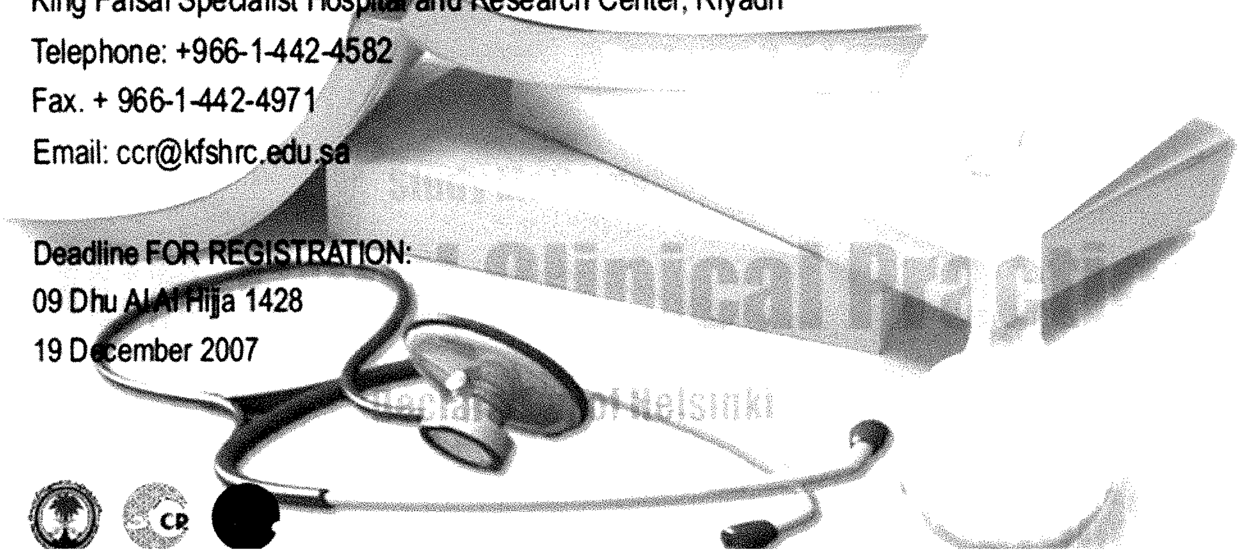

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summary of original articles

TRANSPLANTATION

Experience with 122 consecutive liver transplant procedures at King Faisal Specialist Hospital and Research Center

Saudi Arabia is a leading country in the Middle East in deceased-donor (DDLT) and living-donor liver transplantation (LDLT). Al-Sebayel and colleagues present the experience of the liver transplantation program at King Faisal Specialist Hospital and Research Center for the period from April 2001 to January 2007. During that time, 122 liver transplants were performed, including 77 DDLT and 45 LDLT in 118 patients. Overall patient and graft survival rates were 90% and 80%, respectively. Early expereince indicates there are higher rates of biliary and vascular complications in the LDLT group.

DIABETES AND ENDOCRINOLOGY

Predicting glucose intolerance with normal fasting plasma glucose by the components of the metabolic syndrome

Pei and colleagues tested five models for predicting glucose intolerance in patients with normal fasting plasma glucose.Each model included various components of the metabolic syndrome (MeS). Two models, the MeS model and the fasting plasma insulin model, had the best predictive discrimination in identifying persons with normal fasting plasma glucose at high risk for glucose intolerance.

The utility of fasting plasma glucose in predicting glycosylated hemoglobin in type 2 diabetes

Al-Lawati and Al-Lawati assessed the use of fasting plasma glucose (FPG) in identifying patients with uncontrolled type 2 diabetes by examining the relationship between FPG and glycosylated hemoglobin in 2888 patients ≥ 20 years with type 2 diabetes mellitus. Based on an analysis of data from receiver operating characteristic curves, the authors concluded that FPG may be used to identify uncontrolled patients in situations where glycosylated hemoglobin assays are unavailable.

NEUROLOGY

Impact of hyperglycemia on ischemic stroke mortality in diabetic and non-diabetic patients

Kes and colleagues evaluated the influence of prolonged stress hyperglycemia on stroke mortality in 630 stroke patients with and without diabetes mellitus admitted to the neurological intensive are department with 24 hours of stroke onset. All patients who died within 28 days of hospitalization had prolonged hyperglycemia despite intensive insulin therapy. Non-diabetic patients had a 1.7 times higher relative risk of in-hospital 28-day mortality than patients with diabetes. The results indicate that prolonged stress hyperglycemia in ischemic stroke patients increases the risk of in-hospital 28-day mortaity, especially in non-diabetic patients.

HEMATOLOGY

Age- and body mass index-dependent relationship between correction of iron deficiency anemia and insulin resistance in non-diabetic premenopausal women

In a prospective study, Ozdemir and colleagues evaluated the effect of correction of iron deficiency anemia on insulin resistance in 54 non-diabetic premenopausal women. Fasting insulin levels and HOMA scores decreased signficantly in women of younger age and lower BMI following correction of iron deficiency anemia with oral iron preparations.

LABORATORY MEDICINE

Comparison of the erythrocyte sedimentation rate measured by the Micro Test 1 Sedimentation Analyzer and the conventional Westergren method

Arikan and Akalin compared a new semiautomated technique with a traditional method of measuring the erythrocyte sedimentation rate in 200 hospitalized and ambulatory patients. The new test (Micro Test 1) correlated with the traditional method and was easy to use, had a satisfactory operative practicability, required minimal maintenance, and reduced contact with potential biohazards.

review

Cryptosporidiosis in Saudi Arabia and neighboring countries

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Cryptosporidium is a coccidian protozoan parasite of the intestinal tract that causes severe and sometimes fatal watery diarrhea in immunocompromised patients, and self-limiting but prolonged diarrheal disease in immunocompetent individuals. It exists naturally in animals and can be zoonotic. Although cryptosporidiosis is a significant cause of diarrheal diseases in both developing and developed countries, it is more prevalent in developing countries and in tropical environments. We examined the epidemiology and disease burden of *Cryptosporidium* in Saudi Arabia and neighboring countries by reviewing 23 published studies of *Cryptosporidium* and the etiology of diarrhea between 1986 and 2006. The prevalence of *Cryptosporidium* infection in humans ranged from 1% to 37% with a median of 4%, while in animals it was different for different species of animals and geographic locations of the studies. Most cases of cryptosporidiosis occurred among children less than 7 years of age, and particularly in the first two years of life. The seasonality of *Cryptosporidium* varied depending on the geographic locations of the studies, but it was generally most prevalent in the rainy season. The most commonly identified species was *Cryptosporidium parvum* while *C. hominis* was detected in only one study from Kuwait. The cumulative experience from Saudi Arabia and four neighboring countries (Kuwait, Oman, Jordan and Iraq) suggest that *Cryptosporidium* is an important cause of diarrhea in humans and cattle. However, the findings of this review also demonstrate the limitations of the available data regarding *Cryptosporidium* species and strains in circulation in these countries.

Cryptosporidium is a coccidian protozoan parasite of the intestinal tract that causes severe potentially fatal watery diarrhea in immunocompromised patients and self-limiting but often prolonged diarrheal disease in immunocompetent individuals.[1,2] It can also infect other animal species and thus may be zoonotic.[3,4] The infective form of *Cryptosporidium* is the thick-walled oocyst which is excreted in large numbers in the feces during acute infection. The oocyst is resistant to desiccation and most disinfectants.[5] Volunteer studies have demonstrated that the infective dose can be as low as one oocyst[5] and thus infection is easily spread person-to-person directly or indirectly.

Cryptosporidiosis is a significant cause of diarrheal diseases in both developing and industrialized nations,[6] but several epidemiologic studies have demonstrated that *Cryptosporidium* is more prevalent in developing countries (5% to >10%) than in developed countries (<1% to 3%).[7-9]

In temperate climates cryptosporidiosis accounts for only 1% to 4% of the cases of childhood diarrhea and is usually self-limiting.[5] It can, however, produce devastating diarrhea in HIV-infected individuals who have fewer than 200 CD 4+ lymphocytes/μL of blood.[10] In tropical environments however, cryptosporidiosis is much more prevalent accounting for 4% to 20% of the cases of childhood diarrhea, and children less than two years old have the greatest prevalence of cryptosporidiosis.[5,11] It is associated with high morbidity[8,12-14] and this probably reflects a poorer nutritional status in children in developing countries.[15] Transmission of *Cryptosporidium* spp via contaminated drinking water, outdoor and indoor recreational waters and municipal water is well documented.[16,17] Recently there has been a large water-borne outbreak involving over 800 inhabitants of Bani Hassan in Jordan apparently associated with contaminated drinking water.

Recent molecular epidemiologic studies of cryptosporidiosis have helped us to gain better understanding of the transmission of cryptosporidiosis in humans and the public health significance of *Cryptosporidium* spp. in animals and the environment.

Using genotyping tools, five species of *Cryptosporidium* (*C. hominis, C. parvum, C. meleagridis, C. felis, and C. canis*) have been shown to be responsible for most human infections.[6] The potential for zoonotic infection is a genuine problem since *Cryptosporidium* lacks species specificity.[18] Therefore, domestic and wild species of mammals and birds may be reservoirs of infection for susceptible human individuals, whether they are immunodeficient or immunologically competent.[19] Diarrheal disease is a frequent illness in developing countries, and contributes to the death of 4.6 to 6 million children annually in Asia, Africa and America.[20] Cryptosporidiosis has been recorded as a cause of diarrhea in veterinarians and animal handlers,[21] in bone-marrow transplant recipients,[22] in household contacts of infected patients,[4,23] in homosexual men,[24] in travellers,[25] in children in day care centers[26-29] and in patients with chronic diseases.[30]

Methods for detection of Cryptosporidium spp in feces usually involve microscopic examination of stained fecal smears (modified Ziehl-Neelsen, safranin methylene blue, auramine-phenol), antigen detection (immunofluorescence, ELISA) or genome detection (PCR amplification of the 18S rRNA gene).[5] Each varies in sensitivity and specificity and there is no universally accepted "gold-standard".

There are few published reports of studies on cryptosporidiosis in the Middle East. In Saudi Arabia, diarrheal disease is an important cause of morbidity in children but the contribution made to it by *Cryptosporidium* spp is largely unknown.

The aims of the present review were:

(1) To document the prevalence of *Cryptosporidium* spp in humans and animals in Saudi Arabia and neighboring countries.

(2) To estimate the disease burden.

(3) To examine the age distribution of the cases.

(4) To determine the seasonality of cryptosporidiosis.

(5) To compare the importance of *Cryptosporidium* spp as a cause of diarrhea relative to other enteropathogens.

METHODS

Articles were identified for this review from a multilingual *MEDLINE* search for publications from 1976 to 2006 using the keywords *Cryptosporidium*, and the name of each of the following countries: Saudi Arabia, Kuwait, Iraq, Jordan, Bahrain, Qatar, Yemen, Oman and United Arab Emirates. In addition, the *Annals of Saudi Medicine* and the *Saudi Medical Journal* were handsearched for papers on diarrheal diseases and *Cryptosporidium*.

The studies were grouped into three categories: studies targeting human populations, studies targeting animal populations and studies identifying *Cryptosporidium* species and typing and these were analyzed separately. For each study, the prevalence of *Cryptosporidium* infection was examined initially in patients and compared with controls where a control group was included. Age profile and seasonality were also examined where sufficient data were available. Finally, we reviewed studies in which molecular characterization, typed species and subtyping allele families were available to examine the distribution of the different *Cryptosporidium* species and strains in circulation.

RESULTS

Description of Studies

We found 23 papers published from the region between 1986 and 2006. The prevalence of *Cryptosporidium* infection among humans was addressed by 15 papers,[10,31-44] while the prevalence among animals was addressed by two papers.[42,45] In addition, 5 papers identified the circulating species and reported the molecular characterization of the parasite.[6,36,46-48] One paper reported an outbreak of caprine cryptosporidiosis in the Sultanate of Oman and another examined the prophylactic value of paromomycin in the outbreak.[49,50] Finally, one paper described a case of cryptosporidiosis in a child in Kuwait.[51] The studies included five from Saudi Arabia[10,31,32,45,46] and the remainder from four neighboring countries: Kuwait,[6,33-35,51] Jordan,[36-40,44,47] Iraq[41-43,48] and The Sultanate of Oman.[49,50] Ten of these studies were hospital-based[6,31,33,34,36,40,41,43,48,51] four studies were designed to select inpatient cases only,[33,40,41,51] whereas both inpatients and outpatients were included in another four studies[31,34,36,43] and seven studies targeted hospital outpatients only.[10,32,35,39,44,46,48] In addition seven studies were entirely community-based (Table 1).[37,38,42,45,47,49,50]

Study duration was variable, ranging from 3 months[10,34] to 38 months.[6] The median study duration was 12 months. The ages of the patients surveyed varied significantly, ranging from newborn (0-1 month)[31] to 87 years[38] and even within the same study the age groups ranged from 1 to 87 years.[38] Animal ages were reported only in the study from The Sultanate of Oman[49] and they ranged between two days to over one year.

Detection methods

In most studies fecal specimens were screened by examining stained fecal smears by bright field microscopy and the most common stains used were acid fast stains, (16 studies)[10,32,36-39,41-50] followed by trichrome, (7 studies)[33,34,37-40,44] and safranin methylene blue, (5 studies).[31,33-35,51] Fluorescent microscopy was used to examine fecal smears stained with auramine-phenol, (4 studies).[32,40,49,50] Other techniques such as a direct immunofluorescence assay (DFA) were used in three studies[35,36,47] while polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used in one study from Kuwait.[6] Different techniques used prior to the screening were sedimentation, sugar flotation concentration and direct wet mount preparations.

Prevalence and Seasonality

In humans the prevalence of cryptosporidiosis ranged from 1.0%[32] to 37.3%[36] and seemed to be higher in the studies that targeted infants and children under 7 years old (Table 1) while in animals it was different for different species of animals and the geographic locations of the studies (Table 2). The prevalence of cryptosporidiosis differed depending on the population surveyed. Outpatient studies showed significantly higher prevalences than those where inpatients were included. In addition, mixed inpatient and outpatient studies showed higher prevalences than the community-based studies. The range and median of the outpatient prevalence studies were 1 to 32% and 6.7% respectively, whereas the range and median of combined inpatient and outpatient studies were 1.15 to 37.3% and 5.5% respectively.

Cryptosporidium infection was more common in children less than 7 years of age. Data from eight studies showed that the prevalence of cryptosporidiosis was higher in children less than 7 years old,[10,31,32,35,36,40-42,44] and 4 of these studies showed that the highest prevalence was among children less than 2 years of age.[10,32,35,40]

The seasonal variation in cryptosporidiosis was reported in five studies only. Two studies from Kuwait, which has high temperatures during the summer with a very dry climate and a short cool winter, showed that the highest prevalence was during winter (March and April)[33] or from January to April.[35] The other three studies were from Jordan, which has a relatively wet rainy season from November to April and very dry weather for the rest of the year with uniformly hot dry summers and cool variable winters. The maximum prevalence in the first study, which was done in Irbid City, was undertaken from January to May in the rainy season,[36] while in the two remaining studies, which were done in Badia, the maximum prevalence was reported in the warm months from May to September.[38,39]

Cryptosporidium species and strains identified

The most commonly identified species was described as *Cryptosporidium parvum*, which has been reported from Dammam, Saudi Arabia,[46] Kuwait,[6] Irbid, Jordan,[36] Basra, Iraq[48] and Bani-Kenanah in Jordan (Table 3).[47] *Cryptosporidium hominis* was reported in one study from Kuwait only.[6] Light and immunofluorescent microscopy were used to identify *Cryptosporidium* species in these studies except in the study from Kuwait where advanced molecular tools were used, namely PCR, RFLP and DNA sequencing. It is not possible to assign cryptosporidia to species on the basis of microscopic morphology alone.

In the last study,[6] four subtype allele families (IIa, IId, IIc and IIf) of *Cryptosporidium parvum* were identified and 3 (Id, Ie and Ib) of *Cryptosporidium hominis*. An atypical outbreak of caprine cryptosporidiosis occurred in the Sultanate of Oman in goats ranging in age from two days to adulthood, on a well-managed closed farm.[49] None of the other animals on the farm, including sheep, cows and buffalo were affected. Morbidity approached 100 per cent in goats less than six months of age. Despite intensive supportive care, 238 goats, ranging in age from two days to over one year, died. Cryptosporidia were detected in large numbers in the intestinal contents of dead animals and in faecal smears of animals with diarrhea.

In another study from the Sultanate of Oman, the prophylactic value of paromomycin (an aminoglycoside antibiotic analogous in structure to neomycin)[52] was examined in the same outbreak of caprine cryptosporidiosis.[50]

DISCUSSION

In the 23 studies addressing *Cryptosporidium* infections in Saudi Arabia and neighboring countries, *Cryptosporidium* infection in humans ranged between 1%[32] and 37.3%,[36] while in animals it was different for different species of animals and the geographic locations of studies. It appears that the prevalence of cryptosporidiosis in humans is lower than in animals.[42] Interestingly, the prevalence differed even within Irbid, a city in Jordan, where the prevalence varied from 1.5%[40] to 37.3%.[36] This may be due to methodological differences, as bright field microscopy only was used in most of the studies with its low detection rate compared

Table 1. Cryptosporidium detection rates in Saudi Arabia and neighboring countries.

Country	Period	Detection methods	Number of patients	Age of patients	Number of control	Age	Setting	Prevalence in patients (%)	Prevalence in control (%)	Seasonality	Reference
Saudi Arabia	3/00-5/00	S, DWM, BFM (AFS)	63	17% <1 y	190	<5 y	(O)	32	4.7	NR	(10)
Saudi Arabia	1990	S, BFM (SM-B)	174	25-59 mo	50	0-120 mo	H (I,O)	1.15	0	NR	(31)
Saudi Arabia	11/86-5/87	DWM, S, BFM (AFS), FM (AP)	209 * 112 **	2 y	0	0-12 y >12 y	(O)	1 0	0	NR	(32)
Kuwait	1/88-6/99	DWM, S, BFM (SM-B), TSSP	2205	5-96 mo	0	2 wk to 12 y	H (I)	1.6	0	Winter Mar, Apr	(33)
Kuwait	mid-Jan to mid-Apr 89	S, DWM, BFM (SM-B), TSSP	738 * 413 **	1.25-8 y	0	NR	H (I,O)	1.36 0	0	NR	(34)
Kuwait	9/95-8/97	S, BFM (SM-B), DFA	3549	>2 y	500	3 mo to 13 y	(O)	1.43	0	Winter Jan to Apr	(35)
Jordan	11/00-9/01	DWM, SFC, BFM (AFS), DFA	300	5-7 y	0	0 to 12 y	H (I,O)	37.3	0	Jan to May, the rainy season	(36)
Jordan	9/92-3/93	DWM, S, SFC, BFM (AFS, TSSP)	1000	<9 y	0	6 to 14 y	CB	4	0	NR	(37)
Jordan	9/99-9/01	DWM, S, SFC, BFM (AFS,TSSP)	200	mean 7.5 y	0	1 to 14 y 15 to 87 y	CB	5 3	0	Spring	(38)
Jordan	NR	DWM, S, BFM (AFS, TSSP)	180	NR	100	12 – 84 y	(O)	8.3	0	Warm mo May-Sep	(39)
Jordan	5-8/93	S, BFM (TSSP), FM (AP)	265	<1 y	0	< 5y	H (I)	1.5	0	NR	(40)
Iraq	11/97-5/98	S, BFM (AFS)	40	46- 55 y	175	2 y - 60 y	H (I)	5	1.14	NR	(41)
Iraq	NR	S, BFM (AFS)	60	<6 y	175	4-62 y	CB	5	1.14	NR	(42)
Iraq	1-12/00	S, BFM (AFS)	205	26-35 y	175	2 mo- 65 y	H (I,O)	9.7	1.1	NR	(43)
Jordan	7/92-9/93	DWM, SFC, BFM (TSSP, AFS)	300	<3 y	300	6 mo-6 y	(O)	6.7	1.7	NR	(44)

S: sedimentation, DWM: direct wet mount, BFM: bright field microscope, FM: fluorescent microscope, DFA: direct immunofluorescent assay, SFC: sugar flotation concentration, H: hospital-based, I: inpatient, O: outpatient, CB: community-based, * children, ** adults, SM-B: safranin methylene blue, AP: auramin-phenol, TSSP: trichrom stool smear preparation, AFS: acid fast stain (modified Ziehl-Neelsen, modified Kinyoun's), NR: not reported.

to DFA which is more sensitive. For example, in Irbid the detection rate was 37.3% in the study where DFA was used together with bright field microscopy,[36] while in an other study in the same city where bright field microscopy alone was used, the detection rate decreased to 1.5%.[40]

The finding that most *Cryptosporidium* infections occur among children less than 7 years of age is consistent in most studies in the region and is comparable with the reports from other parts of the world.[53-55] It is possible that the infection rate in these studies would have been higher if more than one stool specimen had been collected from each child because of the intermittent nature of oocyst excretion with this parasite.[56,57] Outpatient studies showed significantly higher prevalences than those where inpatients were included, which may have resulted from the presence of *Cryptosporidium* oocysts in asymptomatic children, some of whom could be considered carriers who act as important reservoirs of the organism and finally a potential source of infection.

Seasonal variations in prevalence have been noted in some studies.[33] Several factors could account for seasonal variations in the occurrence of cryptosporidiosis, including factors affecting the numbers of oocysts present in the environment such as rainfall or agricultural practices, factors affecting oocyst survival, such as humidity or temperature, and factors promoting exposure to oocysts such as contact with animals or attendance at child care centers. However, in most studies, the highest numbers of cases were detected during the rainy season.[58,59] In Kuwait for example the climate is characterized by long dry hot summers (40-50 °C) and short warm winters. There is no rainy season in Kuwait as such. The highest prevalence was during winter (March and April)[33] or from January to April.[35] While in Jordan, which has a relatively moist rainy season from November to April and very dry weather for the rest of the year with hot dry uniform summers and cool variable winters, the maximum prevalence was from January to May. The highest prevalence was during the rainy season in Irbid[36] but in the warm months from May to September in Badia.[38,39]

Few studies have tried to identify the infecting species and *Cryptosporidium parvum* was the most prevalent species identified, but this was with one exception by microscopy alone. *Cryptosporidium hominis* was identified in a study from Kuwait[6] where RFLP was used. Because the majority of these studies were done between 1986 to 1998 no advanced molecular tools were used to identify the infecting species and the researchers depended completely upon microscopy and direct im-

Table 2. Cryptosporidium detection rates among animals in Saudi Arabia and neighboring countries.

Country	City	Period	Duration	Animal type	Detection methods	Number of animals	Prevalence	Reference number
Saudi Arabia	Al-Ahsa region	Oct 2002 to Oct 2003	13 mo	White-cheeked bulbuls	BFM (AFS)	42	28.6 %	(45)
Iraq	Basrah	NR	NR	Domestic animals	S, BFM (AFS)	198	13.6 %	(42)

BFM: bright field microscope, AFS: acid fast stain (modified Ziehl-Neelsen, modified Kinyoun's), S: Sedimentation, NR: not reported

Table 3. Cryptosporidium species identified and subtyping.

Country	City	Species identified	%	Subtyping	Technique	Reference No.
Saudi Arabia	Dammam	*C. parvum*	30	-	S, BFM (E, I, AFS)	(46)
Kuwait	Kuwait	*C. parvum*	94	4 subtype allele families (IIa, IId. IIc, IIf)	SSU rRNA-based PCR-RFLP, 60-KD a glycoprotein-based DNA sequencing tool.	(6)
		C. hominis	5	3 subtype allele families (Id, Ie, Ib)		
Jordan	Irbid	*C. parvum*	37.3	-	DWM, SFC, BFM (AFS), DFA	(36)
Iraq	Basra	*C. parvum*	1	-	S, BFM (AFS)	(48)
Jordan	Bani-Kenanah	*C. parvum*	2	-	BFM (AFS), DFA	(47)

DFA: direct immunoflourescent assay, BFM: bright field microscope, RFLP: restriction fragment length polymorphism, E,I: eosin, iodine stain munofluorescent assay as a screening tool, which calls into question the accuracy of the results. But in the one study where molecular tools such as PCR and RFLP were used, C. *hominis* (5%) and C. *parvum* (95%) were detected.[6]

The distribution of *Cryptosporidium* genotypes in the population is very different worldwide. Studies conducted in Peru, Thailand, Malawi, Uganda, Kenya, and South Africa showed a predominance of C. *hominis* in children or human immunodeficiency virus-positive adults.[60-64] In contrast, most of the patients investigated in Kuwait were infected with C. *parvum*. The only other region where C. *parvum* is more prevalent in humans than C. *hominis* is Europe, where several studies have shown a slightly higher prevalence of C. *parvum* over C. *hominis* in both immunocompetent and immunocompromised persons.[65-68]

The differences in the distribution of *Cryptosporidium* genotypes in humans are considered an indication of differences in infection sources.[68-70] Thus, the predominance of C. *parvum* in a population has been considered to be the result of zoonotic transmission. Indeed, even in areas with a high percentage of infections due to C. *parvum*, massive slaughter of farm animals during foot-and-mouth disease outbreaks can result in a reduction of the proportion of human infections due to C. *parvum*.[71]

Recent subtyping studies have shown that not all C. *parvum* infections in humans are the result of zoonotic transmission.[65,72,73] Among the C. *parvum* GP60 subtype families identified, alleles IIa and IIc (previously known as Ic) are the two most common types. The former has been identified in both humans and ruminants, whereas the latter has been seen only in humans.[65,73,74] In one of the studies included in this review two Kuwaiti children were infected with an allele IIc subtype strain, indicating that anthroponotic transmission of C. *parvum* occurs in Kuwait. Nevertheless, the low proportion of infections due to C. *hominis* suggests that anthroponotic transmission of cryptosporidiosis in Kuwait is probably not as important as in other countries. It is important to note that the other valid taxonomic species have not yet been detected in the region.

Returning to the outbreak of caprine cryptosporidiosis in the Sultanate of Oman, and to determine the reasons for it, it has been noted that the outbreak started during the cooler rainy season and this environmental factor might have imposed a stress responsible for the epizootic. However the rainy season may be associated with other factors, such as the enhanced survival of the organism in the environment or the seasonal variability of antibody levels observed in goats. Jonson et al.[75] observed an increase in incidence of enteric and respiratory diseases in goats during the rainy season in north-east Brazil and associated it with lower levels of serum antibodies recorded during the wet season than during the dry hot season. It has also been reported that goats who do not receive colostrum or are separated from their mothers and fed artificially, are more likely to develop cryptosporidial infections.[76-78] The kids in the Omani study were all suckled by their mothers and there was no indication that they had not received adequate quantities of colostrum. No immediate source of the infection was apparent. The water supply was not tested for cryptosporidia, but it seemed unlikely to have been the source because no other animals were affected and the treated water supply for the animals was the same as that for human consumption. It was a closed herd and the possibility that the infection was brought in from outside could therefore be ruled out.

In conclusion, future studies should focus predominantly on those in the age group <7 years, as this is consistent with the findings of previous studies in the region and elsewhere. The period of future studies should be at least 12 months to be able to detect any seasonal variation. Wherever possible, molecular techniques should be used for typing *Cryptosporidium* in order to provide valuable information about all circulating *Cryptosporidium* species and strains in the region. Finally, we recommend that physicians be aware of *Cryptosporidium* as a cause of diarrhea in children and that procedures for the diagnosis of this parasite be included in the routine diagnostic procedure for diarrheal stool specimens in all laboratories. This is particularly important since there is now an effective drug, nitazoxanide, available for therapy.[79]

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original article

Experience with 122 consecutive liver transplant procedures at King Faisal Specialist Hospital and Research Center

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BACKGROUND: Saudi Arabia is a leading country in the Middle East in the field of deceased-donor liver transplantation (DDLT) and living-donor liver transplantation (LDLT). We present out experience with DDLT and LDLT at King Faisal Specialist Hospital and Research Center (KFSHRC) for the period from April 2001 to January 2007.

PATIENTS AND METHODS: We performed 122 LT procedures (77 DDLTs and 45 LDLTs) in 118 patients (4 re-transplants) during this period of time.

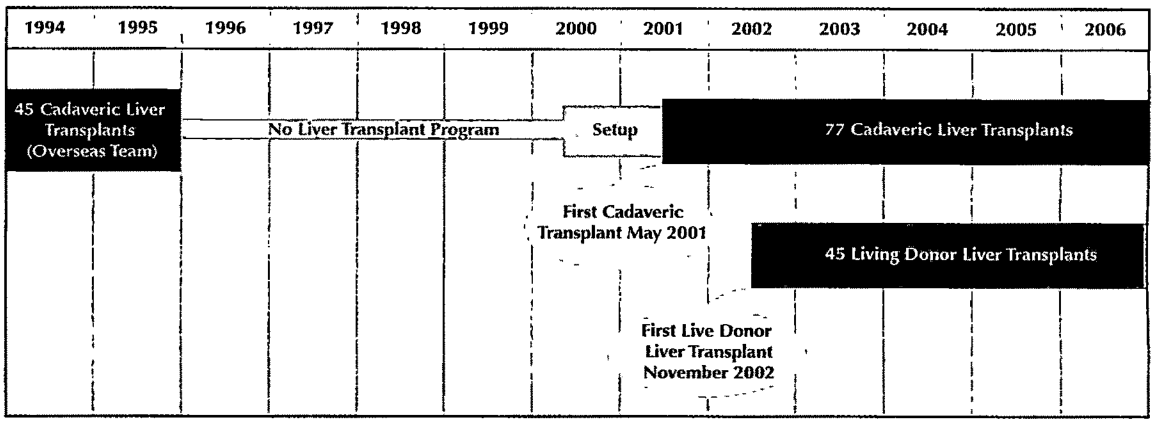
RESULTS: The number of adult and pediatric procedures was 107 and 11, respectively. The overall male/female ratio was 66/52 and the median age of patients was 43 years (range, 2-63 years). In the DDLT group, the median operating time was 8 hours (range, 4-19), the median blood transfusion was 6 units (range, 0-40), and the median hospital stay was 13 days (range, 6-183). In the DDLT group, after a mean follow-up period of 760 days (range, 2-2085), the overall patient and graft survival rate was 86%. In the LDLT group, the median operating time was 11 hours (range, 7-17), the median blood transfusion was 4 units (range, 0-65), and the median hospital stay was 15 days (range, 7-127). In the LDLT group, and after a mean follow-up period of 685 days (range, 26-1540), the overall patient and graft survival rates were 90% and 80%, respectively with no significant difference in patient and graft survivals between groups. Biliary complications were significantly higher in LDLT compared to DDLT ($P<0.05$). Vascular complications were also significantly higher in LDLT compared DDLT ($P<0.05$).

CONCLUSIONS: Both DDLT and LDLT are being successfully performed at KFSHRC with early experience indicating a higher rate of biliary and vascular complications in the LDLT group.

The Kingdom of Saudi Arabia is the leading country in the Middle East in the field of deceased-donor liver transplantation (DDLT).[1-5] Since the first DDLT in 1990, more than 300 DDLTs were performed in Saudi Arabia, divided mostly between two main liver transplantation (LT) centers. More recently, living-donor liver transplantation (LDLT) has been introduced in Saudi Arabia in an attempt to overcome the severe shortage of cadaveric organs in the Kingdom. To date, more than 200 LDLTs have been performed in Saudi Arabia, divided between three main LT centers.[6-9] Along with Egypt, Saudi Arabia was one of the leading countries in the field of LDLT in the Middle East.[10-12] The LT program at King Faisal Specialist Hospital and Research Center (KFSHRC) was first established in 1994. At that time, 45 DDLTs were performed by a visiting LT team from abroad, but unfortunately that program was suspended in 1996 due to logistical difficulties (Figure 1). In April 2001, the LT program at KFSHRC was re-started by a local team in an attempt to meet the rapidly growing need for LT in Saudi Arabia.[13] We present the KFSHRC experience in the last 6 years with both DDLT and LDLT.

PATIENT AND METHODS

In the period between April 2001 and January 2007 122 liver transplant procedures (77 DDLTs and 45 LDLTs) were performed in 118 patients (including 4 re-transplants) at KFSHRC. All 77 DDLTs procedures were performed by the local team using cadav-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45 Cadaveric Liver Transplants (Overseas Team)
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Setup
77 Cadaveric Liver Transplants
First Cadaveric Transplant May 2001
45 Living Donor Liver Transplants
First Live Donor Liver Transplant November 2002

Figure 1. Evolution of the liver transplant program at KFSHRC.

eric organs retrieved from brain-dead heart-beating cadaveric donors who fulfilled the strict clinical criteria for brainstem death diagnosis set by the Saudi Center for Organ Transplantation. Almost all DDLT recipients were adults; only 3 pediatric patients underwent DDLT. Double veno-venous bypass was used in six of the DDLT recipients. Roux-en-Y hepaticojejunostomy was used for biliary reconstruction in 12 DDLT recipients while duct-to-duct anastomosis was used in the remaining 65 DDLT recipients.

For the LDLT group, outside assistance was required in the first two LDLTs, while the local team alone without outside assistance performed all the following 43 LDLT procedures. The left lateral segment (segments 2-3) was used in 8 pediatric LDLT recipients, the entire left lobe without the caudate (segments 2-4) was used in one pediatric LDLT recipient, and the whole right lobe (segments 5-8) was used in the 36 adult LDLT recipients. The middle hepatic vein was included with the right liver graft in only 3 LDLT recipients. In all LDLT procedures, microvascular surgeons performed the hepatic artery anastomosis using a microscope. Roux-en-Y hepaticojejunostomy (REY) was used for biliary reconstruction in 6 LDLT recipients, duct-to-duct anastomosis was used in 38, and combined REY and duct-to-duct anastomoses were performed in one patient. All biliary anastomoses were performed using interrupted 6/0 absorbable sutures without stenting. Re-transplantation using a cadaveric organ was necessary in 4 LDLT recipients.

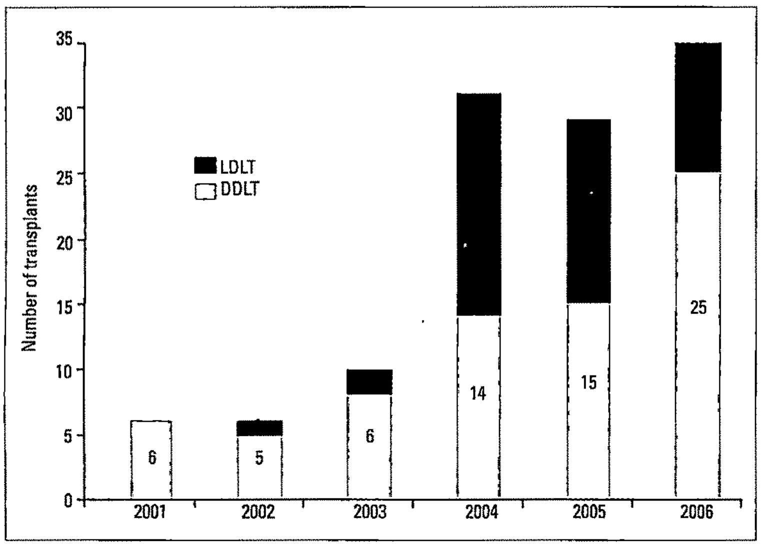

Figure 2. Number and types of liver transplants performed each year since April 2001.

All donors for LDLT were related to their recipients. The graft-recipient weight ratios ranged from 0.8% to 1.7%; the remaining liver volume in all donors was ≥30% of the calculated whole liver volume; and macrovesicular steatosis in all grafts was ≤20% (estimated by routine percutaneous liver biopsy in all donors). All donors were carefully assessed and approved by a social worker, a psychologist, and at least one senior member of the surgical team.

Our postoperative immunosuppression regimen was mainly FK506 and steroids. Mycophenolate mofetil was used in conjunction with FK506 for various indications, including renal impairment, neurotoxicity, autoimmune etiology, and hepatitis C virus (HCV) recurrence. In most cases, steroids were stopped after 3 months, but continued in those with autoimmune etiology. A few patients were converted from calcineurin inhibitors to sirolimus for various reasons including nephrotoxicity, neurotoxicity, and posttransplant lymphoproliferative disorders. Lamivudine and hepatitis B virus (HBV) immunoglobulins were used in four patients who had HBV infection-related cirrhosis.

A Kaplan-Meier analysis was used to measure the

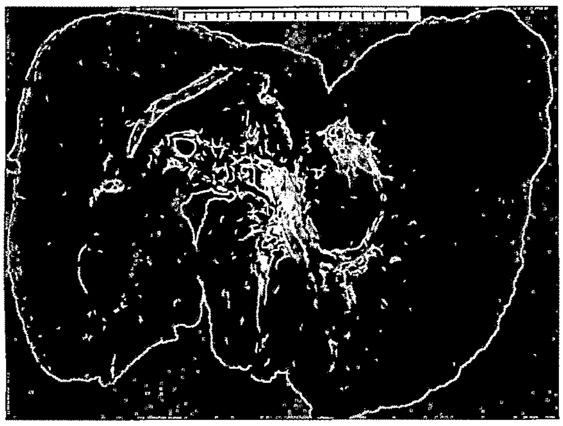

Figure 3. Liver explant showing hepatitis C virus-induced liver cirrhosis and small hepatocellular carcinoma.

Table 1. Indications for liver transplantation in 122 recipients.

Indication	No	%
Hepatitis C virus	35	29%
Viral hepatitis + hepatocellular carcinoma	21	17%
Hepatitis B virus	10	8%
Autoimmune hepatitis	15	12%
Cholestatic liver disease	11	9%
Cryptogenic cirrhosis	10	8%
Primary hyperoxaluria	4	3%
Wilson's disease	5	4%
Glycogen storage disease	2	2%
Budd-Chiari syndrome	1	1%
Re-transplantation	4	3%
Others	4	3%
Total	**122**	

survival function, the log-rank test was used to compare between the survivals in different groups, and the Chi-square test was used to compare the frequency of complications in different groups. SPSS software was used for statistical analysis. A P value of < 0.05 was taken as significant.

RESULTS

The numbers of LTs performed per year is shown in Figure 2. The overall male/female ratio was 66/52; the adult/pediatric ratio was 107/11, and the median age was 43 years (range, 2-63 years). Indications for liver transplantation in 122 LT recipients are shown in Table 1. Liver cirrhosis due to viral hepatitis with or without hepatocellular carcinoma (HCC) was the main indication for LT in our study group (Figure 3).

In the DDLT group, the male/female ratio was 38/39; the adult/pediatric ratio was 74/3; the median age was 44 years (range, 11-63 years); the median operating time was 8 hours (range, 4-19), the median blood transfusion was 6 units (range, 0-40), and median hospital stay was 13 days (range, 6-183). The overall patient and graft survival rate was 86% after a mean follow-up period of 760 days (range, 2-2085). The 11 deaths in the DDLT group were due to primary graft non-function in 4 patients, central pontine myelinolysis in one patient, recurrent hepatitis C virus cirrhosis in 3 patients, chronic rejection in one patient, recurrent HCC in one patient, and recurrent cholangiocarcinoma in one patient.

In the LDLT group, the male/female ratio was 29/16; the adult/pediatric ratio was 36/9; the median age was 47 years (range, 1.5-63 years); the median operating time was 11 hours (range, 7-17), the median blood transfusion was 4 units (range, 0-65), and the median hospital stay was 15 days (range, 7-127). The overall patient and graft survival rates were 90% and 80%, respectively, after a mean follow-up period of 685 days (range, 26-1540). Re-transplantation using cadaveric organ was necessary in 4 LDLT recipients. Graft failure and patient deaths were due to hepatic artery thrombosis in 2 cases, biliary complications in one patient, uncontrollable bleeding in one patient, portal vein thrombosis in 2 cases, and small-for-size syndrome in 3 patients.

For the live liver donors, the male/female ratio was 34/11; the median age was 25 years (range, 18-42), the median hospital stay was 6 days (range, 4-14), and only two donors required intra-operative blood transfusion. After a median follow-up period of 529 days (range, 8-1354), a total of 28 morbidities were encountered in 17 donors (37.8%) of which 9 donors (20%) had serious complications (Table 2). No donor death was encountered in our experience.

Biliary complications were significantly higher in the LDLT group compared to the DDLT group–25.6% vs. 2.6% respectively ($P<0.05$). Vascular complications were also significantly higher in the LDLT group compared with the DDLT group–8.9% vs. 2.6% respectively ($P<0.05$).

The overall (DDLT and LDLT) patient and graft survival after a mean follow-up period of 736 days (range, 6-2089) were 90% and 86%, respectively (Figure 4). The overall and actuarial survival rates in both DDLT and LDLT groups are summarized in Table 3. In the short-term follow-up there was significantly

Table 2. Donor morbidities in 45 live liver donors.

Recorded Complication	No.	Graft Used	Management	Outcome
Sever liver dysfunction	2	Rt Lobe	Supportive	Recovered
Incisional hernia	2	Rt Lobe(1); LLS (1)	Laparoscopic mesh repair under GA	Recovered
Bad scar	3	Rt Lobe	Scar revision	Satisfied
Bile leak, collections, and sepsis	1	Rt Lobe	ERCP and stenting under sedation	Recovered
Biloma	1	LLS	Percutaneous drainage	Recovered
Skin dehiscence	1	Rt Lobe	Secondary closure under local anesthesia	Recovered
Pressure-induced alopecia areata	3	Rt Lobe	None	Recovered
Neurapraxia of the right arm	1	Rt Lobe	Physiotherapy	Recovered
Bad scar	2	Rt Lobe(1); LLS (1)	Refused scar revision	Satisfied
Incisional pain	4	Rt Lobe	Pain control	Responded
Abdominal discomfort	5	Rt Lobe(4); LLS (1)	Symptomatic treatment	Responded
Depression	3	Rt Lobe	Psychological counseling	Responded

LLS: left lateral segment; GA: general anesthesia; Rt: Right.

Table 3. Overall and actuarial survival rates in 122 liver transplant recipients.

Type	No.	Overall survival	Actuarial survival May 2001 – Jan 2007					
			Patient survival			Graft survival		
			1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
DDLT	77	86%	91%	79%	79%	91%	79%	79%
LDLT	45	89%	88%	87%	87%	79%	79%	79%
Overall	**122**	**87%**	**90%**	**83%**	**83%**	**86%**	**79%**	**79%**

DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation.

poorer graft survival rate in the LDLT (log-rank test, $P<0.05$); however, in long-term follow-up there was no statistical significant difference between the two groups in either patient survival or in graft survival (Figures 4-6). This can be simply explained by the use of cadaver organs to re-transplant failed LDLT grafts.

DISCUSSION

The Saudi Center for Organ Transplantation was successfully established in 1985,[14] and this paved the way for the launch of DDLT programs in our country. The first DDLT in Saudi Arabia was performed in 1990, and to date more than 300 of these operations have been performed with good success.[1] As mentioned, the LT program at KFSHRC lapsed for a period, and was reactivated by our current surgical team in 2001. We have since performed 77 DDLT procedures with excellent outcomes and a survival rate that is comparable to rates at other experienced LT centers. However, soon after restarting our DDLT program, we were faced with the major barrier of a severe cadaveric organ shortage for LT in Saudi Arabia. This shortage is due to many complex logistical problems in all steps of the cadaveric donation process, including donor identification, reporting, diagnosis, management, documentation, and obtaining consent.[14-20] This distressing scarcity of cadaveric donor organs, together with the increasing number of patients dying on our LT waiting list has significantly limited our ability to expand our LT program. Therefore, we were forced to consider adopting LDLT, which seemed the only logical way forward in our situation. Our initial reluctance to undertake LDLT was fueled by the many ethical questions that are generated by the concept of live liver donation: Is it ethical to ask a person to donate part of his or her liver to save the life of a loved one? Can the donor truly give

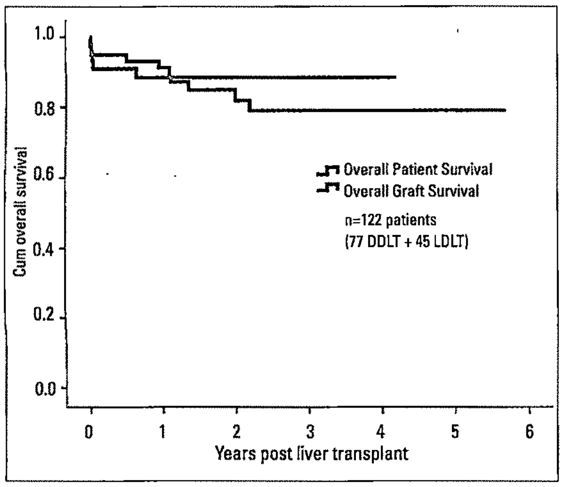

Figure 4. Overall patient and graft survival after mean follow-up of 736 days.

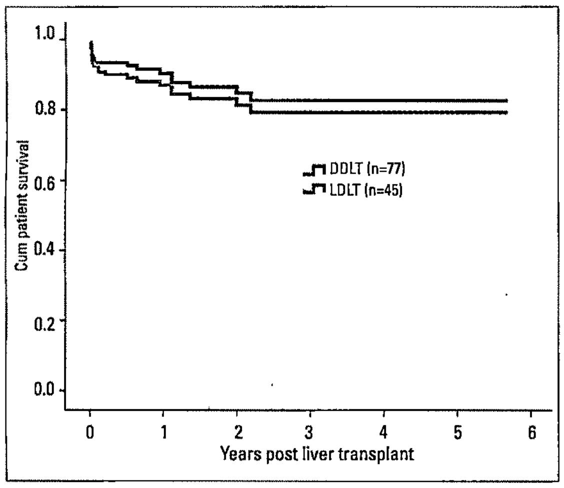

Figure 5. Cumulative patient survival in deceased-donor and live-donor transplatations.

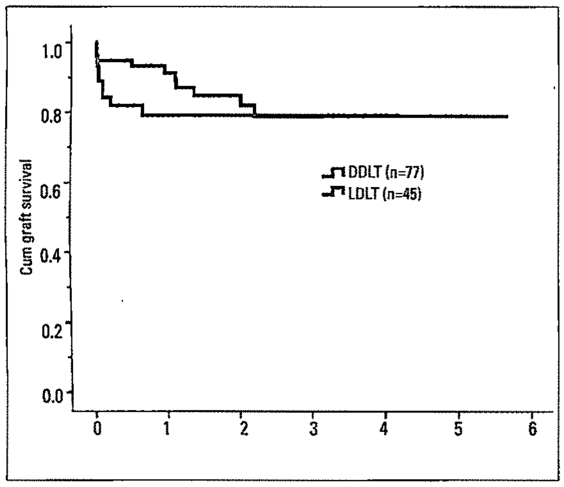

Figure 6. Cumulutaive graft survival in deceased-donor and live-donor transplantations.

informed consent under such circumstances? Would it not be considered "emotional blackmail"? Is it ethical to subject a healthy person to a major operation with potential morbidity and mortality in order to save the life of another? Another major concern about live donation is the likelihood of organ trafficking, which cannot be ignored, especially in regions with high poverty rates. Despite these moral dilemmas, the team came to the conclusion that our patients have the right to be offered all available treatment options, including LDLT, and that, as a team, we must take all necessary precautions to respect donor interests and ensure donor safety. To date, we have performed 45 LDLTs and our overall survival rates are comparable to other international LDLT programs, especially when the learning curve process is considered.[21-24] The rate of biliary complications in the LDLT group was significantly high when compared to DDLT, which again has been reported by other centers that perform LDLT.[23,25] Despite this higher rate of biliary and vascular complications in the LDLT group, the overall 1-, 3-, and 5-year graft and patient survival rates are similar to the DDLT group, which reflects the successful management of those complications by a multidisciplinary team approach.

In our early experience with LDLT at KFSHRC, we were astonished by how difficult it is to find living donors who fulfill our criteria for liver donation. Many candidates have been rejected for a variety of reasons, including unexpected pathology (steatosis and viral disease) and failure to pass psychosocial evaluation.[26] Therefore, we have come to the conclusion that LDLT is not the answer to all of our challenges, and that this procedure can help alleviate the problem of organ shortage, but cannot replace DDLT in Saudi Arabia. We believe that we should focus our efforts on identifying and fixing the different problems that have led to the decline in the number of available cadaveric donors. By doing so, we hope to considerably increase the cadaveric organ pool for LT in our country.

In conclusion, both DDLT and LDLT are being performed successfully at KFSHRC. The shortage of cadaveric donors and the difficulty of finding suitable donors for LDLT remain the main factors that limit expansion of our emerging LT program. Therefore, efforts should be directed toward increasing the number of available cadaveric donors. Until the number of cadaver donors rises, expansion of the LDLT component of our program may be the only way to save patients from dying on the waiting list.

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original article

Predicting glucose intolerance with normal fasting plasma glucose by the components of the metabolic syndrome

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BACKGROUND: Surprisingly, it is estimated that about half of type 2 diabetics remain undetected. The possible causes may be partly attributable to people with normal fasting plasma glucose (FPG) but abnormal postprandial hyperglycemia. We attempted to develop an effective predictive model by using the metabolic syndrome (MeS) components as parameters to identify such persons.

SUBJECTS AND METHODS: All participants received a standard 75-g oral glucose tolerance test, which showed that 106 had normal glucose tolerance, 61 had impaired glucose tolerance, and 6 had diabetes-on-isolated postchallenge hyperglycemia. We tested five models, which included various MeS components. Model 0: FPG; Model 1 (clinical history model): family history (FH), FPG, age and sex; Model 2 (MeS model): Model 1 plus triglycerides, high-density lipoprotein cholesterol, body mass index, systolic blood pressure and diastolic blood pressure; Model 3: Model 2 plus fasting plasma insulin (FPI); Model 4: Model 3 plus homeostasis model assessment of insulin resistance. A receiver-operating characteristic (ROC) curve was used to determine the predictive discrimination of these models.

RESULTS: The area under the ROC curve of the Model 0 was significantly larger than the area under the diagonal reference line. All the other 4 models had a larger area under the ROC curve than Model 0. Considering the simplicity and lower cost of Model 2, it would be the best model to use. Nevertheless, Model 3 had the largest area under the ROC curve.

CONCLUSION: We demonstrated that Model 2 and 3 have a significantly better predictive discrimination to identify persons with normal FPG at high risk for glucose intolerance.

Type 2 diabetes mellitus (T2DM) is a serious chronic disease with disordered carbohydrate metabolism that places a heavy burden on health services and patients due to its morbidity and mortality. The prevalence T2DM is continuously growing worldwide.[1,2] Remarkably, glucose intolerance (eg., impaired glucose intolerance [IGT] and diabetes) is frequently asymptomatic and the delay from disease onset to clinical diagnosis may exceed at least 4 to 7 years.[3] Strikingly, tissue damage progresses before diagnosis.[4-7] Therefore, early diagnosis and intervention are important in reducing the burden of diabetic complications. In one study, it was estimated that up to 50% of persons with diabetes were undetected or newly diagnosed.[8-10] One of the possible causes may be attributable to a normal fasting plasma glucose (FPG) but abnormal postprandial hyperglycemia, i.e., IGT or diabetes-on-isolated postchallenge hyperglycemia (DM-on-IPH) may also be responsible.[11]

The prevalence of IGT in Taiwan established in 1996 was 15.5%, which was higher than the prevalence of diabetes (9.2%).[12] However, in Taiwan, about 40% of diabetics have not yet been diagnosed.[13] Moreover, the mortality of T2DM is growing and was the fourth leading cause of death in Taiwan in 2002[14] with about a 6.3-fold increase over a period of 30 years.[15] Thus, we are encouraged to establish a simple and efficient predictive model to reduce the incidence of T2DM by early prediction and intervention.

The diagnostic criteria of diabetes was revised by the American Diabetes Association (ADA)[16] in 1997. The main modifications emphasized using only FPG to diagnose diabetes and lower the cutoff point to 7.0 mmol/L. Furthermore, a new category of "impaired fasting glucose" (IFG) was introduced. Subsequently, the World Health Organization (WHO) criterion for the diagnosis of diabetes[17] was also published. It retained the lower cutoff for FPG and, at the same time, suggested that the oral glucose tolerance test (OGTT) was still a useful method for diagnosing diabetes. However, after both criteria have been reported, many studies have found that the concordance between them was not so good.[18-23] Furthermore, according to ADA criteria, whether persons with normal FPG are truly non-diabetic is an emerging problem. It could be noted that people with either DM-on-IPH[11] or diabetes-on-isolated fasting hyperglycemia are difficult to detect by the 1997 ADA criteria. To solve these problems, many authors have suggested different methods to increase the sensitivity to detect diabetes, such as the level of glycated hemoglobin[24] or a predictive risk score model.[25]

Metabolic syndrome (MeS) is a cluster of metabolic factors, including central obesity, hypertension, dyslipidemia, and glucose intolerance. People with MeS are found to have a high risk for cardiovascular disease and T2DM. The central pathophysiology of MeS is generally agreed to be insulin resistance,[26-28] which is also central to T2DM.[29] The term "MeS" was coined by WHO in 1998 as an attempt at eraly detection of subjects at high risk for diabetes and cardiovascular diseases.[16] Three years later, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) had also provided another similar, but simple and clinically useful definition of MeS.[30]

In this study, we were interested in and focused on persons with normal FPG who had either normal glucose tolerance (NGT), IGT, or DM-on-IPH. We conducted a binary logistic regression analysis to obtain a model to estimate the probability of having dysglycemia (i.e., IGT and DM-on-IPH in our study). The components of MeS were put into the proposed models. A receiver-operating characteristic (ROC) curve[31] was used to determine the predictive discrimination power of these models with the hope of obtaining a simple and efficient predictive model that could be widely acceptable in clinical or health care settings to identify subjects at high risk for glucose intolerance.

SUBJECTS AND METHODS

A total of 513 participants were enrolled and received the standard 75-g OGTT in Tri-Service General Hospital from 1998 to 2001. Subjects were either self-referred or referred by health professionals, seeking a screening for diabetes. They had no history of diabetes in the past. After excluding frank diabetes and IFG, only 424 cases were suitable for further study. Among them, 82 were classified as IGT (defined as 2-h PG during OGTT between 7.8 and 11.1 mmol/L and FPG < 6.1 mmol/L), another 6 as DM-on-IPH (defined as FPG < 6.1 mmol/L and 2-h plasma glucose (2-h PG during OGTT ≥ 11.1 mmol/L).[23] However, due to incomplete data on family history or other parameters, only 106 subjects with NGT, 61 with IGT and 6 with DM-on-IPH were available for this study. None of the patients had significant medical or surgical history. Before the study, they were instructed by the doctors and dietitians not to receive any medication known to affect glucose or lipid metabolism and to stay on a stable diet for at least one week before the study. On the day of the visit, each subject had a complete routine work-up to rule out the presence of cardiovascular, respiratory, renal or endocrine disorders. The study had been approved by the hospital ethics committee, and the purpose and the potential risks of the study were explained to the subjects before obtaining their written consent to participate.

On the day of the test, a standard 75-g OGTT was carried out for 3 hours after a 12-h overnight fast. Blood samples were obtained for the determination of glucose and insulin concentrations at baseline (time 0 min) and 30-minute intervals for 3 hours. Other than the OGTT, homeostasis model assessment (HOMA) was also used to estimate the insulin sensitivity (HOMA-IR=fasting plasma insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5). HOMA is a mathematical model based on glucose and insulin interaction in different organs, including the pancreas, liver, and peripheral tissues.[32] The model determines insulin sensitivity or insulin resistance.[32,33] Application of HOMA has also been used in epidemiological studies.[32,34]

Plasma was separated from blood within 1 hour and stored at −30°C until analyzed. Plasma glucose was determined by the glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Spring Instrument Company, Inc., Yellow Spring, Ohio, USA). Insulin[35] was measured by a commercial radio-immunoassay kit (Coat-A-Count insulin kit, Diagnostic Products Corporation, Los Angeles, California, USA).

Both triglycerides (TG) and total cholesterol (TC)

Table 1. Anthropometric and metabolic characteristics of study subjects.

Demographic data	NGT	Dysglycemia
Number	106	67
Sex (M/F)	50/56	37/30
Age	35.4±1.2	41±1.6*
BMI (kg/m^2)	22.8±0.4	24.7±0.5*
SBP (mmHg)	115.1±1.3	124.9±2.3*
DBP (mmHg)	74.7±1.0	80.7±1.5
TC (mmol/ L)	3.6±0.9	4±0.1
TG (mmol/ L)	1.3±0.1	1.7±0.1*
HDL-C (mmol/L)	2.74±0.23	0.77±0.04
FPG (pmol/ L)	5.1±0.04	5.3±0.1
2-h PG	5.6±0.1	9.1±0.2*
FPI (pmol/ L)	48.4±2.6	85.5±14.7*
HOMA-IR	1.6±0.9	2.8±0.5*

NGT, normal glucose tolerance group; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; 2-h PG, 2-hour plasma glucose during after 75-g OGTT; HOMA-IR, homeostasis model assessment of insulin resistance. * versus NGT group, $P< 0.05$; Data are shown as mean±SE.

were measured using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) concentration was determined by an enzymatic cholesterol assay method after dextran sulfate precipitation.

Since there were only 6 subjects with DM-on-IPH and the purpose of our study was to predict glucose intolerance only, we combined both the IGT group and DM-on-IPH group into one as a "dysglycemia group". Although there are a number of MeS definitions, the NCEP ATP III-defined MeS criteria has been widely applied in clinical and epidemiological research. Therefore, we employed these criteria in our study. However, since we did not have data on waist circumference, we used BMI instead.

Using binary logistic regression analysis we put all interesting factors into the model for model selection. Five models were proposed to identify normal and abnormal glucose metabolism. Each model included the different components of the MeS. The five models were as follows:

- Model 0: FPG
- Model 1 (clinical model): family history, FPG, age and sex
- Model 2 (the MeS model): all risk factors in Model 1 plus TG, HDL-C, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- Model 3 (insulin was added for evaluating the effect of insulin level on the model): all risk factors in Model 2 plus fasting plasma insulin (FPI)
- Model 4 (HOMA-IR was added): all risk factors in Model 3 plus HOMA-IR.

For Model 0, the FPG was forced into the model. The 95% confidence intervals were also calculated for the binary logistic regression analysis. The Hosmer-Lemeshow test was used to assess the goodness of fit of these models. Calculations were performed using the SPSS (10.0) statistical package (SPSS Inc., Chicago, IL, USA). A P-value (two-sided) < 0.05 was considered to be significant. For each individual in every model, an estimated probability of an abnormal event (occurrence of dysglycemia) was also calculated. We then used the estimated probability to predict whether a subject was at high risk for dysglycemia (see the appendix). A plot of the ROC curve, which is a line diagram with the sensitivity plotted vertically with the false positive rate on the horizontal axis, and is determined by the trapezoidal rule, was used to choose the cutoff of values. The diagonal line represents results no better than chance. The ROC curve is a mathematical method used to assess the predictive discrimination of a test.[31] The statistical significance of differences in areas under ROC curves between any two models were estimated by likelihood ratio testing.

RESULTS

Table 1 shows the demographic data of the study subjects. From the selection criteria, it is not surprising that all subjects had normal FPG. The dysglycemic group was older and had a higher BMI, SBP, TG, 2-h PG, FPI and HOMA-IR than the NGT group. All data were adjusted for age and BMI.

Model 0 had only one risk factor (FPG) and was regarded as the "baseline model". The area under the ROC curve was significantly greater than the area under the curve of the diagonal reference line (Panel A, Figure 1), which means that the prediction rate could be improved significantly even with use of FPG alone.

Table 2 presents the areas under the ROC curves, their Hosmer-Lemeshow goodness-of-fit statistics, and tests of the statistical significance of the differences between various models by the likelihood ratio test. When compared to Model 0, all of the other 4 models have a larger area under the ROC curve (better prediction rate). Moreover, by putting more variables into the

Table 2. Area under the receiver-operating characteristic (ROC) curve and their comparisons for models predicting dysglycemia.

Models* and model comparisons	Area under the ROC curve (95% CI),%	*P* value (Hosmer-Lemeshow)**	*P* values for model comparisons (likelihood ratio tests)***
Models			
0	64.8 (56.1-73.6)	0.001	
1	67.3 (59-75.6)	0.303	
2	74.8 (67.3-82.3)	0.045	
3	76.8 (69.5-84.1)	0.658	
4	76.6 (69.3-83.8)	0.767	
Comparisons between models			
0-1			0.01
1-2			0.003
2-3			0.02
3-4			0.414

*Model 0: FPG; Model 1 (clinical data): family history, FPG, age and sex; Model 2 (the MeS model): all risk factors in Model 1 plus TG, HDL-C, BMI, SBP and DBP; Model 3 (insulin was added for evaluating the effect of insulin level on the model): all risk factors in Model 2 plus FPI; Model 4 (HOMA-IR was added): all risk factors in Model 3, plus HOMA-IR.

***P* values calculated by using the Hosmer-Lemeshow goodness-of-fit test.

****P* values for test of difference in areas under two ROC curves; calculated by the likelihood ratio test.

model, a larger area under the ROC curve could be obtained. In other words, we improved the prediction rate of the models. However, no significant difference was noted between Model 3 and Model 4, implying that adding the parameter HOMA-IR into Model 3 does not further increase the area under ROC curve.

The different ROC curves are shown in Figure 1 panel B. The arrow indicates the arbitrarily selected risk score cutoff (0.39) of Model 3, which has a sensitivity and specificity of 70.1% and 73.6%, respectively, with the area under ROC curve of 76.8% (95% CI, 69.5-84.1%).

DISCUSSION

This is the first study to examine the performance of a simple multivariable risk score model using routinely collected data related to MeS as a screening tool for undetected glucose intolerance in Taiwanese persons. Persons with normal FPG may be considered "non-diabetic". However, several studies have reported that up to half of diabetics are undiagnosed.[8-10,36] Compared to diabetes, IGT is even more difficult to diagnose since OGTT is not routinely done.[37] Although IGT is generally recognized as a "pre-diabetic" state, it still carries an increased risk for developing cardiovascular complications similar to diabetes.[38-40] Therefore, in practice, to identify individuals with dysglycemia it is important for clinicians so that preventive interventions can be given early.

OGTT is costly, time consuming, inconvenient and rarely used in an ordinary clinical setting, but it can identify a subject with normal FPG who may have glucose intolerance (e.g. IGT and DM-on-IPH). Therefore, there is a need to develop a widely accepted method for identifying subjects at high risk for glucose intolerance so that early intervention with lifestyle and/or pharmacologic management can be implemented to prevent or delay diabetes.[41-43]

In our study, we proposed five models with multiple variables related to the components of the MeS, with Model 0, the baseline model, including FPG only. All five models (Figure 1, panel B), including Model 0, were statistically significant ($P<0.05$) meaning that all models for prediction would improve diagnostic performance. We did not use WC in our study because we did not measure it at that time. Although waist circumference is suggested by NCEP ATP III as a tool to define adiposity, its superiority can be questioned.[30] First, Ford et al[44] showed that the correlation coefficient between WC and BMI is high, up to 0.88 in different sex, age or ethnic groups. Secondly, measurement of height and weight is more easily done in a routine clinical setting and is more accurate than measurement of WC. Indeed, there were many different methods to measure WC, each of which would yield various absolute values.[45] Thirdly, one study using the measurement of insulin-mediated glucose disposal has demonstrated a similar relationship between insulin resistance and adiposity, regardless of whether assessed by BMI or WC.[46] Finally, both BMI and WC have been shown to be closely related to the cardiovascular risk factors in Taiwanese persons.[47] For these reasons, we could justify the use of BMI instead of WC in our study and we believe that the findings are not substantially altered.

From the ROC curve of Model 1, the optimum cutoff point we arbitrarily selected was 5.43 mmol/L for FPG, which is less than the ADA criteria (5.6 mmol/L). This yields a sensitivity and specificity of 55.2% and 81.1%, respectively. Interestingly, the predictive discrimination of all of the other multivariable models outperforms Model 0. That is, each of the areas under ROC curves of Model 1 to 4 was greater than the area under the ROC curve of Model 0. The most significant increment in the area was noted between Model 1 and Model 2 (67.3% to 74.8%). This implies that adding components of MeS into the model will significantly increase the predictive discrimination power.

HOMA-IR is an important quantitative method for

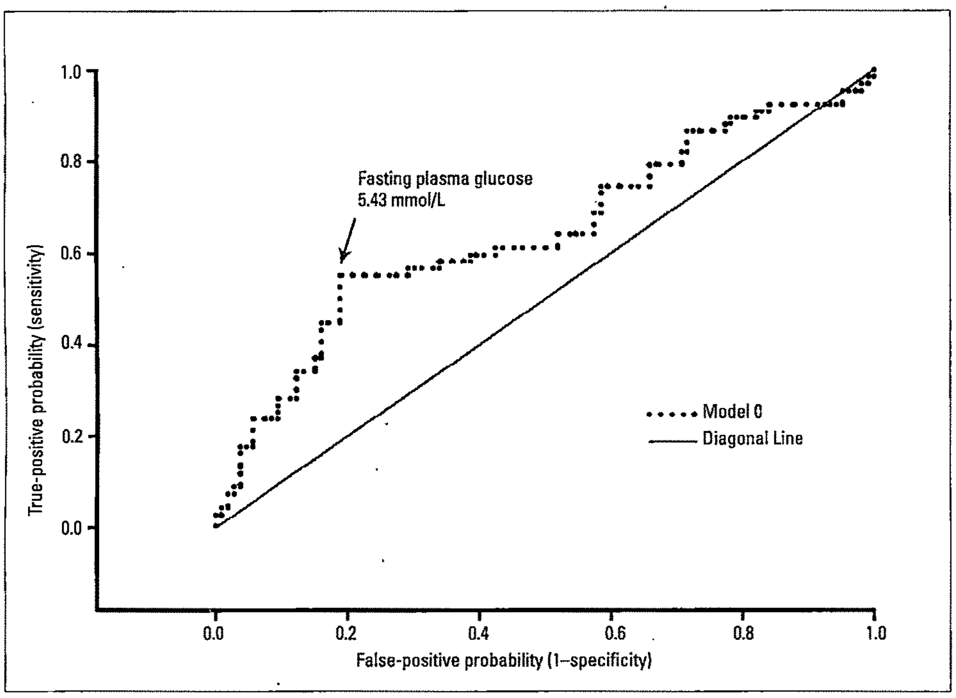

Figure 1A. Receiver operating characteristic curve of Model 0 (see methods for a description of the model). The optimum cutoff (5.43 mmol/L) is shown with an arrow (sensitivity: 55.2%, specificity: 81.1%; area: 67.3%).

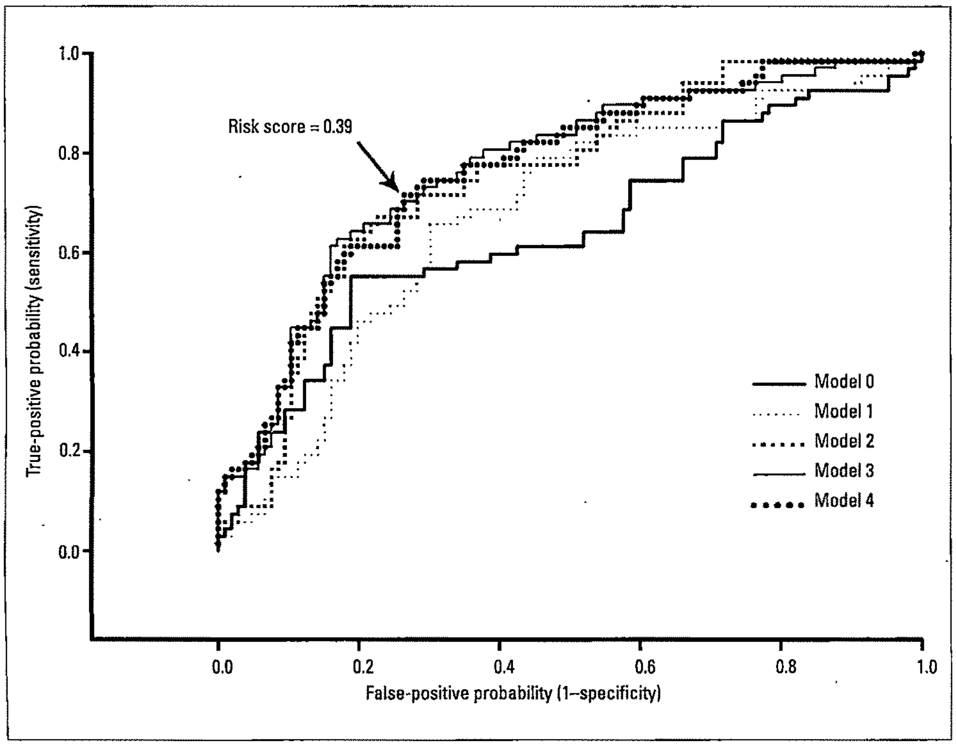

Figure 1B. Receiver operating characteristic curves of the five models, Models 0-4 (see METHODS for a description of the models). The arrow indicates the arbitrarily selected risk score cutoff (0.39) of Model 3 (sensitivity, 70.1%; specificity, 73.6%; area, 76.8%).

the measurement of insulin resistance.[32] In our study, no significant change in the area under the ROC curve was noted after adding the parameter of HOMA-IR into Model 4. This is not surprising because the HOMA-IR is derived from a simple equation multiplying FPI and FPG. Since Model 3 has both of FPI and FPG, Model 4 with HOMA-IR should not be significantly different from Model 3.

Although putting the FPI level into Model 3 will further increase the area under the ROC curve up to 76.8%, it should be noted that FPI is not routinely measured in a routine health check-up. Additionally, the cost is also too high. Thus, considering that there is no significant difference between Model 2 and Model 3 in performance and the simplicity of Model 2, Model 2 seems to be the most appropriate predictive model to be used in the current clinical and health care settings. Nevertheless, it should be noted that Model 3 has the largest area under the ROC curve. The cutoff will vary depending on workload and attitudes to false positives and false negatives. In Model 3, a cutoff of the risk score of 0.39 is suggested, which gives a sensitivity and specificity of 70.1% and 73.6%, respectively, with the area under the ROC curve of 76.8% (95% CI, 69.5-84.1%).

Although many other screening tools for undiagnosed diabetes have also been developed in earlier studies, our study specifically attempts to focus on those persons with normal FPG and evaluates their chance of developing glucose intolerance (dysglycemia). The Herman et al[48] study was the first one that tried to prospectively identify individuals at increased risk for diabetes by using a simple questionnaire. They proposed a classification tree incorporating age, sex, history of delivery of a macrosomic infant, obesity, sedentary lifestyle, and family history of diabetes. In their study, the sensitivity was 79% and the specificity was 65%, which were somewhat better than our model. This might be due to some of the risk factors used in their tree model being not included in our models. In this study, our main purpose was to develop a simple multivariable model consisting of readily available clinical measurements, especially related to the MeS, most of which are routinely obtained anyway. Therefore, we did not put parameters such as macrosomic infant and sedentary lifestyle into our models because they are not routinely collected in the clinical setting. Also, in their study, they tried to identify diabetes, which represents more severe abnormal glucose tolerance than IGT in our study. When a larger range of the risk factors (in this case, blood glucose) are put into the model, the sensitivity and specificity are more accurate and the area under ROC curve larger.

Griffin et al[49] developed the Cambridge risk score, another means of determining risk of diabetes. Other than common risk factors (age, gender, BMI), they considered a history of smoking, and steroid and antihypertensive medication use as risk factors. This model yielded an area under ROC curve of 80%. In another study done by Park et al[50] with the same model, the area under the ROC curve was 65.7%. However, steroid use is not a common condition in Taiwan and, again, this history is not available in a routine health check-up. Therefore, we did not put this risk factor into our model. Although the area under the ROC curve in our Model 2 (74.8%) did not have as good a performance as in the Griffin's study,[49] it is better than the Park study.[50]

Of all the literature reviewed, Stern's model[25] was most similar to ours. In their study, the full model had the same risk factors as our model except for TC, low-density lipoprotein cholesterol (LDL-C), 2-h PG and sibling history. Their prediction model had an area under the ROC curve of around 85%, which is higher than that of our model. The area under the ROC curve in other similar studies using different models ranged from 67% to 80%.[49,51,52] In the above comparisons, our model has also a relatively better performance in sensitivity and specificity. Since most general practical clinics have been computerized, it would be convenient to identify persons with a positive score on Model 2 or 3 with the assistance of a personal computer.

Our study has some limitations. We have to stress that the case cohort in our study was not selected independently and randomly and the population size was also relatively small. Therefore, further randomized and prospective larger-scale studies are needed to validate our predictive model. Nevertheless, to the best of our knowledge, our study is the first one to suggest that using an MeS-related multivariable model could predict subjects with glucose intolerance, including IGT. We hope our study can stimulate the initiation of a larger population-based study.

In conclusion, we have demonstrated that the predictive performance of Model 2 and 3 using the components of the MeS, which are routinely available data, and FPI is significantly better than FPG and/or family history alone. Without much effort, subjects with normal FPG at high risk for glucose intolerance could be identified early in the clinical setting, and then followed by the 75-g OGTT for further diagnosis. We hope that our predictive model can be validated by a large-scale longitudinal cohort study in the future and accepted widely by general practitioners.

Appendix:

The following are parameter estimates for the Model 3 in this study:

$p=1/(1+e^{-x})$, where $X=-7.094+0.132(FPG)+0.242(sex)-0.091(FH)+0.039(age)+0.07(BMI)+0.014(SBP)-0.001(DBP)+0.474(TG)-0.116(HDL\text{-}C)+0.008(FPI)$. In this equation, p, the probability of developing diabetes; FPG, fasting plasma glucose in mmol/L; sex=1 if female, 0 if male; FH=0 if no parents have diabetes, 1 if one of the parents has diabetes; age is in years; BMI, body mass index in kg/m^2; SBP, systolic blood pressure in mm Hg; DBP, diastolic blood pressure in mm Hg; TG, triglycerides in mmol/L; HDL-C, high-density lipoprotein cholesterol in mmol/L; FPI, fasting plasma insulin in pmol/L.

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original article

The utility of fasting plasma glucose in predicting glycosylated hemoglobin in type 2 diabetes

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BACKGROUND: Access to glycosylated hemoglobin (HbA1c) assays in clinical practice remains limited. We investigated the relationship of fasting plasma glucose and HbA1c to determine optimal glucose levels for predicting HbA1c.

PATIENTS AND METHODS: We retrospectively analyzed data on 2888 patients with type 2 diabetes mellitus aged ≥20 years using a linear regression of HbA1c against fasting plasma glucose. A receiver-operating characteristic analysis was used to determine optimal cut-points for fasting glucose in relation to HbA1c, area under the curve, sensitivity and specificity, and 95% confidence intervals (CI) for each cut-point.

RESULTS: The mean (standard deviation) for the age of patients was 52±11.6 years. The average HbA1c was 8.9±2.46% and mean fasting plasma glucose was 10.1±3.62 mmol/L. The prevalence of HbA1c ≥7.0% and >6.5% was 76% and 82%, respectively. Overall, fasting plasma glucose and HbA1c were linearly correlated (r=0.62, *P*=0.001). A fasting plasma glucose of >9.0 mmol/L predicted HbA1c ≥7.0% with an area under the curve = 0.807 (95% CI, 0. 0.794 to 0.821), while fasting plasma glucose >8.2 mmol/L predicted HbA1c >6.5%, with an area under the curve = 0.805 (95% CI, 0.791 to 0.818). The sensitivity of both cut-points was 64.5% and 70.7%, the specificity was 82.7% and 76.4%, the positive likelihood ratio was 3.73 and 2.99, and the positive predictive value was 92.2% and 93.2%, respectively.

CONCLUSION: When HbA1c determination is not available, fasting plasma glucose levels may be used to identify patients with uncontrolled type 2 diabetes and initiate timely intensification of therapy to avoid long-term complications of diabetes.

Both the Diabetes Control and Complications Trial (DCCT)[1] and the United Kingdom Prospective Diabetes Study (UKPDS)[2] have demonstrated unequivocally that tight control of blood glucose can significantly reduce progression of complications in both type 1 and type 2 diabetes mellitus. Glycosylated hemoglobin (HbA1c) has been used as a "gold standard" for mean glycemia and as a measure of risk for the development of diabetes-related complications.[3,4] The American Diabetes Association (ADA) suggested HbA1c levels less than 7% as a goal for optimal glycemic control,[5] while the American Association of Clinical Endocrinology (AACE)[6] and the International Diabetes Federation (IDF) set a lower target (6.5% or less).[7]

The ADA recommends that HbA1c be tested 2 to 4 times annually, based on the patient's glycemic control. However, several barriers to HbA1c testing have been identified at the primary and managed care level,[8-10] including physicians' and patients' awareness and the relative cost of the test. In this study we aimed to determine the relationship of fasting plasma glucose (FPG) measurements obtained routinely in primary health care outpatient clinics to simultaneously measured HbA1c levels. We also investigated optimal FPG levels which best predict HbA1c ≥7.0% or >6.5% to guide physicians in intensifying antidiabetic therapy.

SUBJECTS AND METHODS

We retrospectively analyzed the data of 2888 patients with type 2 diabetes mellitus, aged 20 years or older, attending mini-diabetes clinics at 21 of 24 primary health care centers, in the capital, Muscat (Oman). These centers cover a population of over 600 000 and nearly

8000 diabetic patients are on their National Diabetes Registers. About 14% of patients had their HbA1c tested more than once during the study period, and were included in the analysis, giving the total number of 3359. Patients with missing data were excluded from the analysis. The study included patients attending over the period from July 2003 to June 2004.

Venous blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA), labeled and transferred in cold boxes filled with ice to a tertiary hospital laboratory. There, samples were stored at 2 to 8°C as recommended by the manufacturer for analysis on every Monday of the week. Samples were analyzed using Roche/Hitachi 902 instruments (Boehringer Mannheim, Tokyo, Japan). According to the manufacturer, HbA1c determination in this instrument is based on turbid metric inhibition immunoassay for hemolyzed whole blood and uses the detergent tetradecyltrimetylammonium bromide (TTAB) as the hemolysing reagent to eliminate interference from leukocytes. All hemoglobin variants that are glycated at the N-terminal of the B-chain and have antibody recognizable regions identical to that of HbA1c are determined by the assay. Reagents and calibration kits were supplied by the same manufacturer. Prior to analysis of every batch, the instrument was checked for calibration.

Plasma-calibrated fasting blood glucose was determined in primary health centers using One Touch II (Johnson & Johnson) glucose meters. On every request for analysis of HbA1c, primary care physicians were required to state the fasting capillary blood glucose level that was determined on the same day of venous blood collection for HbA1c.

A linear regression analysis was performed to study the relationship between FPG and HbA1c using Stata (version 9.1, Stata Corporation, TX, USA). Receiver-operating characteristic (ROC) curves were generated to determine optimal FPG cut-points predicting HbA1c ≥7.0% and >6.5%, using MedCalc (version9), which also calculates the area under the curve (AUC), sensitivity, specificity, likelihood ratio and positive predictive values with 95% confidence intervals (CI). The larger the AUC the more accurate the test; an associated P-value <0.05 was considered statistically significant. Unlike predictive values, likelihood ratios are not affected by the prevalence of the attribute and can be used to summarize how many times a subject with a specified FPG cut-point is more (or less) likely to have HbA1c ≥7.0% (or >6.5%) than a subject without that FPG value. For any test, likelihood ratios above 1 increase the probability that the "disorder" is present (in this case HbA1c ≥7.0% or >6.5%), and likelihood ratios <1 decrease the probability that the "disorder" is present.[11] Permission to conduct the study was ob-

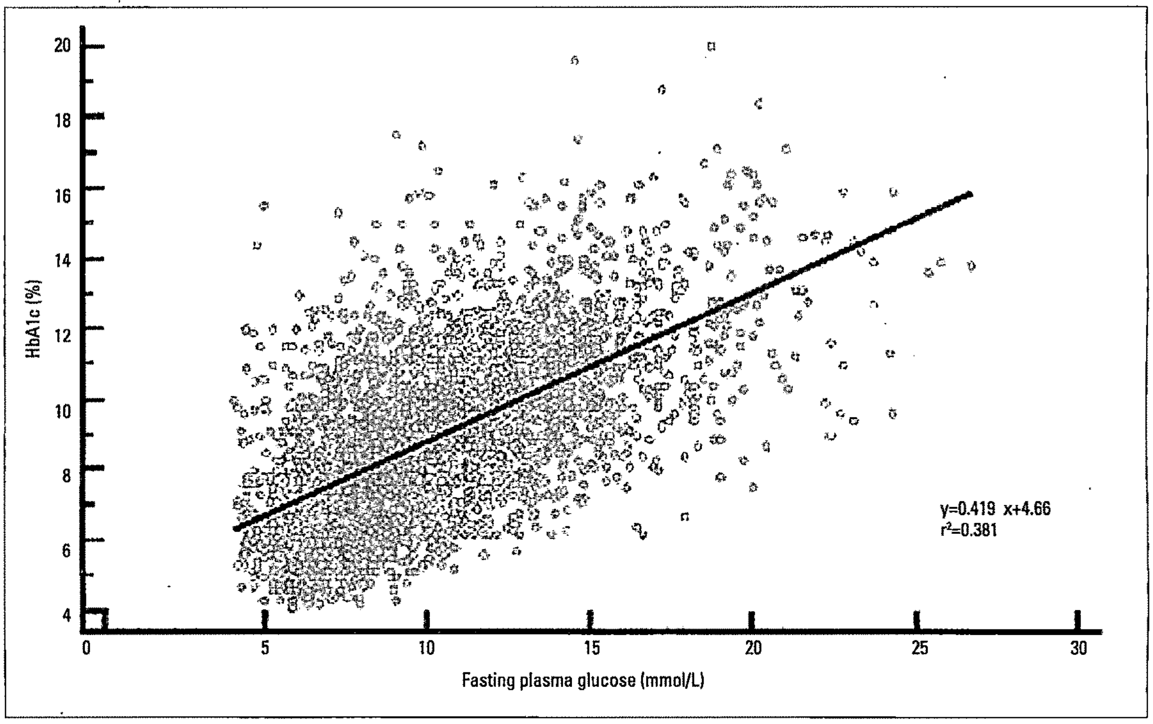

Figure 1. Relationship between fasting plasma glucose and HbA1c, among 3359 Omani patients with type 2 diabetes mellitus.

tained from the research and ethical committee within the Ministry of Health.

RESULTS

The mean age (SD) of the 2888 patients was 52 (11.6) years. The average HbA1c was 8.9% (2.46%) (normal range, 4% to 6%) and the mean FPG was 10.1 (3.62) mmol/L. Over 76% (95% CI, 74.5% to 77.5%) of patients had HbA1c ≥7% and nearly 82% (95% CI, 80.6% to 83.3%) had HbA1c>6.5%. Figure 1 shows that FPG was significantly correlated with HbA1c ($r=0.62$, $P=0.001$). An ROC curve analysis revealed that FPG was a significant predictor for HbA1c ≥7.0% and >6.5%, with a similar AUC: 0.807 (95% CI, 0.794 to 0.821) and 0.805 (95% CI, 0.791 to 0.818), respectively. An FPG >9.0 mmol/L was depicted as the best cut-point to predict HbA1c levels ≥7.0% (Figure 2) and FPG >8.2 mmol/L (not shown) for HbA1c >6.5%. Both cut-points had a sensitivity of 64.5% and 70.7%, specificity of 82.7% and 76.4%, positive likelihood ratios of 3.73 and 2.99, and positive predictive values of 92.2% and 93.2%, respectively (Table 1).

DISCUSSION

This study highlights the relation between FPG and glycated hemoglobin used to monitor long-term glycemic control among Omani patients with type 2 diabetes mellitus. Multi-center prospective studies have demonstrated that intensive treatment and improved control of diabetes can prevent or slow the development of its complications. The DCCT results suggest that a 10% decrease in HbA1c (from 8.0% to 7.2%) can result in up to a 40% to 50% reduction in microvascular complications in individuals with type 1 diabetes.[12] Similarly, the United Kingdom Prospective Diabetes Study determined that an 11% reduction in HbA1c will lower the risks of microvascular complications by 25% and myocardial infarction by 16% in patients with type 2 diabetes.[2]

In many diabetes clinics in developing countries, HbA1c may not always be available for the clinician to permit therapy adjustment. For example, in two university teaching hospitals, only 40% and 50% of patients had HbA1c registered on their medical records within the previous year.[13,14] On the other hand, FPG is often routinely measured in diabetes clinics for all patients prior to consultation with the physician. Thus the utility of FPG would increase if the physician can use this value to predict the glycemic index of the patient with diabetes in an outpatient setting. Our study provides specific FPG cut-points that may be used to guide clinical decisions to intensify antidiabetic therapy in the absence of HbA1c or home glucose monitoring values. Nearly two-thirds (64.5%) of our patients with FPG >9.0 mmol/L were correctly identified to have HbA1c ≥7.0% while FPG >8.2 mmol/L identified nearly three-quarter (72%) of those with HbA1c >6.5%.

Rohlfing et al, in their analysis of glucose profiles and HbA1c of the DCCT, found that an FPG of 9.5 mmol/L corresponded to an HbA1c of 7%, and 7.5 mmol/L corresponded to 6%.[15] El-Kebbi et al[16] reported that an FPG >9.2 mmol/L best predicted HbA1c >8.0% in a population of African Americans, with a sensitivity of 80% and specificity of 83%. When casual postprandial plasma glucose was used, a lower cut-point (8.3 mmol/L) was reported to predict both HbA1c >6.5% or ≥7.0%.[17]

Although many studies have used statistical methods to predict HbA1c from FPG, the validity of this approach in assessing glycemic control in patients with diabetes has been questioned.[18] Bouma et al[19] showed in 1020 patients with type 2 diabetes that HbA1c is difficult to predict from FPG values: only 66% of the patients with HbA1c <7.0% were identified by FPG values <7.8 mmol/L. They concluded that predicting

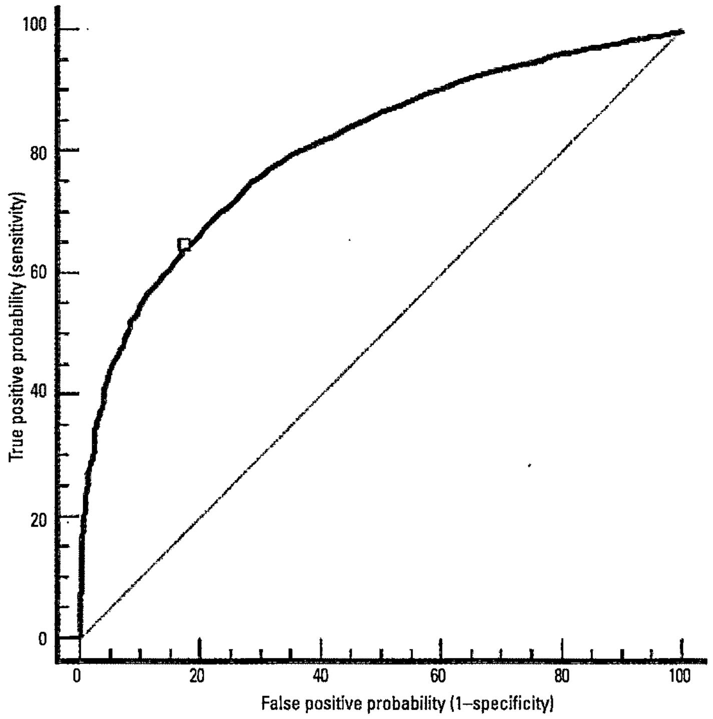

Figure 2. Receiver-operating characteristic curve showing the performance of fasting plasma glucose in predicting glycosylated hemoglobin (HbA1c) in 3359 individuals with type 2 diabetes mellitus in Oman. The diagonal interrupted reference line (AUC=0.50) defines points where a test is no better than chance in identifying individuals with diabetes.

Table 1. Optimal cut-points predicting glycosylated hemoglobin (HbA1c) levels using fasting plasma glucose (FPG) with associated sensitivity, specificity, positive likelihood ratio, positive predictive value and area under the ROC curves.

	Optimal FPG	Sensitivity (95% CI)	Specificity (95% CI)	+LR	PPV (%)	AUC (95% CI)
HbA1c ≥ 7.0%	> 9.0 mmol/l	64.5 (62.6 to 66.3)	82.7 (79.9 to 85.3)	3.73	92.2	0.807 (0.794 to 0.821)
HbA1c > 6.5%	> 8.2 mmol/l	70.7 (69.0 to 72.4)	76.4 (72.8 to 79.7)	2.99	93.2	0.805 (0.791 to 0.818)

ROC, receiver-operating characteristic; CI, confidence interval; +LR, positive likelihood ratio; PPV, positive predictive value; AUC, area under the curve.

HbA1c changes from FPG changes is even more difficult. Similarly, Avignon et al,[20] demonstrated in 66 type 2 diabetic patients that early post-lunch (2:00 pm) and extended post-lunch (5:00 pm) plasma glucose correlated significantly and independently with HbA1c, but that of pre-breakfast and pre-lunch plasma glucose did not. Nonetheless, the ADA states that "FPG is somewhat better than post-prandial glucose in predicting HbA1c, especially in type 2 diabetes".[21] Other studies have shown that, in such patients, fasting blood glucose determinations (at intervals of weeks to months) provide a better measure of long-term glycemia than in patients with type 1 diabetes.[22,23]

In addition to the statistical methods used to estimate long-term glycemic control, standard methods such as self-monitoring of blood glucose, venous blood glucose and HbA1c remain the main stay of diabetes care to achieve a specific level of glycemic control and to prevent hypoglycemia. Physicians ought to use standard methods of investigation when providing diabetes care and encouraging patients to perform self-monitoring blood glucose measurements as needed.

This study documents for the first time that the majority of patients (76%) with type 2 diabetes in primary care in Oman exhibit poor glycemic control (HbA1c ≥7.0%) according to the ADA guidelines.[5] The prevalence of poor control increases to 82% if the AACE target is applied (HbA1c >6.5%). These results are consistent with two studies from Saudi Arabia and one from Lebanon where poor control was prevalent among 73%, 77%, and 72% of patients with diabetes, respectively.[13,14,24] In comparison, two National Health and Nutrition Examination Surveys, conducted between the periods 1988-1994 and 1999-2000 in the US, reported that 56% and 63% patients had poor glycemic control, respectively.[25] Higher rates of poor control were reported from other studies among African Americans (77%) and Finnish people (75%).[17,26] This clearly highlights the urgent need for intervention to improve diabetes care in developing and developed countries.

Our study has some limitations. First, adopting an FPG cut-point of >9.0 mmol/L as a predictor of HbA1c ≥7.0% would result in about 35.5% of individuals being "missed" as they will be considered to have good glycemic control when in fact they do not (false negative). Similarly, 17.3% of people may be at risk of hypoglycemia as they may be subjected to more intense anti-diabetic therapy when in fact having good glycemic control (false positive). Nonetheless, hypoglycemia tends to be uncommon and mild in patients with type 2 diabetes, even in settings in which intensive diabetes therapy is guided by treatment algorithms based on glucose levels obtained during office visits.[27] In addition, in the presence of high levels of poor control (as is the case in many settings), hypoglycemia may not be a common complication.

The above relation between FPG and HbA1c was derived without adjustment for other confounders like age, gender, body mass index, smoking status, type and duration of diabetes. Including such variables may result in more accurate cut-points, yet it would have compromised the objective of this study, which was to increase the utility of FPG in clinical practice by making it simple.

Finally, the accuracy of glucose measurement instruments used in primary care during the study period was not evaluated by simultaneous matched measurement of venous blood samples. However, several studies have demonstrated a high degree of accuracy of such instruments when compared with the laboratory reference over a broad range of glucose concentrations.[28]

In conclusion, we have identified a cut-point for FPG that may be used as an indicator of glycemic control in patients with type 2 diabetes when current HbA1c levels or home blood glucose monitoring records are not available.

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original article

Impact of hyperglycemia on ischemic stroke mortality in diabetic and non-diabetic patients

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BACKGROUND: Previous studies suggest that infarct expansion may be responsible for increased mortality after stroke onset in patients with prolonged stress hyperglycemia. Therefore, we evaluated the influence of prolonged stress hyperglycemia on stroke mortality in patients with and without diabetes.
PATIENTS AND METHODS: For 630 stroke patients admitted to the neurological intensive care department within 24 hours of stroke onset, we correlated mean blood glucose levels (MBGL) at admission and 72 hours after admission in diabetic and non-diabetic patients with final outcome. Blood glucose levels higher then 6.1 mmol/L (121 mg/dL) were treated as hyperglycemia.
RESULTS: Of 630 patients (mean age 71 ± 6), 410 were non-diabetic (mortality, 25%) and 220 patients were diabetic (mortality, 20%). All patients who died within 28 days of hospitalization had prolonged hyperglycemia (at admission and after 72 hours, despite insulin therapy). The unadjusted relative risk of in-hospital mortality within 28 days for all stroke patients was 0.68 (95% CI, 0.14-1.9) for non-diabetic patients and 0.39 (95% CI, 0.27-1.56) for diabetic patients. The unadjusted relative risk of in-hospital mortality within 28 days in ischemic stroke in patients with MBGL > 6.1-8.0 mmol/L (121-144 mg/dL) at admission and after 72 hours was 1.83 (95% CI, 0.41-5.5) for non-diabetic patients and 1.13 (95% CI, 0.78-4.5) for diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 times higher relative risk of in-hospital 28-day mortality than patients with diabetes.
CONCLUSION: Prolonged stress hyperglycemia in ischemic stroke patients increases the risk of in-hospital 28-day mortality, especially in non-diabetic patients.

Stroke is leading cause of disability and death in developed countries. Therefore it is of great interest to evaluate all factors that could affect the acute phase of stroke and change 30-day mortality and functional outcome. One of these factors is prolonged stress hyperglycemia, which is still not exactly defined and possibly not well treated.[1-3]

Hyperglycemia (blood glucose level >6.1mmol/L or 121 mg/dL) is common in early phase of stroke, even in patients without a previous diagnosis of diabetes mellitus. It has been found in two thirds of all stroke patients and in almost half of ischemic stroke patients.[3,4] A recent meta-analyses of prospective and case-control studies confirmed the importance of early stress hyperglycemia as a predictor of stroke outcome, but debate continues as to whether the effect is independent of pre-existing diagnosis of diabetes or initial stroke severity. It is still not clear what cut-off value of the mean blood glucose level (MBGL) should be considered safe in diabetic and non-diabetic patients.[5] New and sophisticated techniques such as MR spectroscopy, CT, PET and conventional MRI findings still have inconclusive results.[6] Therefore we evaluated data on stroke patients admitted to the Neurological Intensive Care Department to estimate the influence of prolonged stress hyperglycemia on short-term mortality in both diabetic and non-diabetic patients.

PATIENTS AND METHODS

We included the data of 630 stroke patients admitted to the Neurological Intensive Care Department within 24 hours of stroke onset in the year 1999 (according to previous medical documentation). The standardized workup for stroke included: blood hematology and chemistry, blood cholesterol and glucose levels, electrocardiography (ECG), chest X-ray, carotid and vertebral color Doppler flow imaging (CDFI) and transcranial Doppler (TCD), brain computed tomography (brain CT), angiography and spinal tap with cerebrospinal fluid (CSF) analyses in selected patients

The definition of stroke (according to WHO criteria) was "rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours, unless interrupted by surgery or death, with no apparent cause other than a vascular origin". By definition, patients with transient ischemic attacks were excluded. The criterion for stroke classified as ischemic stroke or intracerebral hemorrhage was verification of the clinical picture on a brain CT scan or spinal tap. Short-term 30-day case fatality was counted as the proportion of deaths in hospitalized stroke patients. Blood glucose levels at admission and during next 72 hours that were higher than 6.1 mmol/L (121 mg/dL) were treated as hyperglycemia.

Data are presented as absolute numbers (expressed as mean ± SD) and percentages. Statistical analysis was performed with StatSoft Inc for Windows. Proportions were used in most tables and figures. The unadjusted relative risk and 95% confidence interval for mortality in all stroke patients and in ischemic and hemorrhagic stroke patients separately in hyperglycemic versus non-hyperglycemic patients, and hyperglycemic diabetic and non-diabetic patients was calculated. χ^2 test was used to test differences in proportions. Statistically significant values were considered for $P<0.05$ and $P<0.01$.

RESULTS

There were 630 patients (mean age, 73±15.6 years), including 267 men (mean age, 72±14.8 years) and 363 women (75±16.3) admitted to the Neurological Intensive Care Department in the year 1999. Women were 5 years older, but there were no statistically significant differences according to age in the patients with stress hyperglycemia.

Crude 30-day short-term mortality was 26% (164 patients), while 30-day short-term mortality in patients with stress hyperglycemia versus patients without stress hyperglycemia was 25% in non-diabetic patients and 20% in diabetic patients. There were 101 non-diabetic patients (16% of all patients) with stress hyperglycemia that died within 30 days of hospitalization versus 46 patients with pre-existing diabetes who died within 30 days (7% of all patients). There were more than double number of non-diabetic patients versus diabetic patients who died with verified stress hyperglycemia. Statistically significant sex differences were not found so we pooled the data.

There was no statistically significant difference in MBGL between non-diabetic patients and diabetic patients who did not have stress hyperglycemia and who recovered after stroke. In the group of patients with stress hyperglycemia who died within 30 days of hospitalization there were statistically significant differences in MBGL between the non-diabetic patients and the diabetic patients. The first group had a lower MBGL at admission and after 72 hours ($P<0.05$). Patients in both groups (diabetic and non-diabetic) varied in MBGL (6.1-36 mmol/L at admission, 6.1-24 mmol/L after 72 hours), but most of them (in both groups) had a MBGL between 6.1-8.0 mmol/L (121-144 mg/dL).

The unadjusted relative risk of in-hospital mortality within 30 days for all stroke patients was 0.68 (95% CI, 0.14-1.9) for non-diabetic patients and 0.39 (95% CI. 0.27-1.56) for diabetic patients (Figure 1). The un-

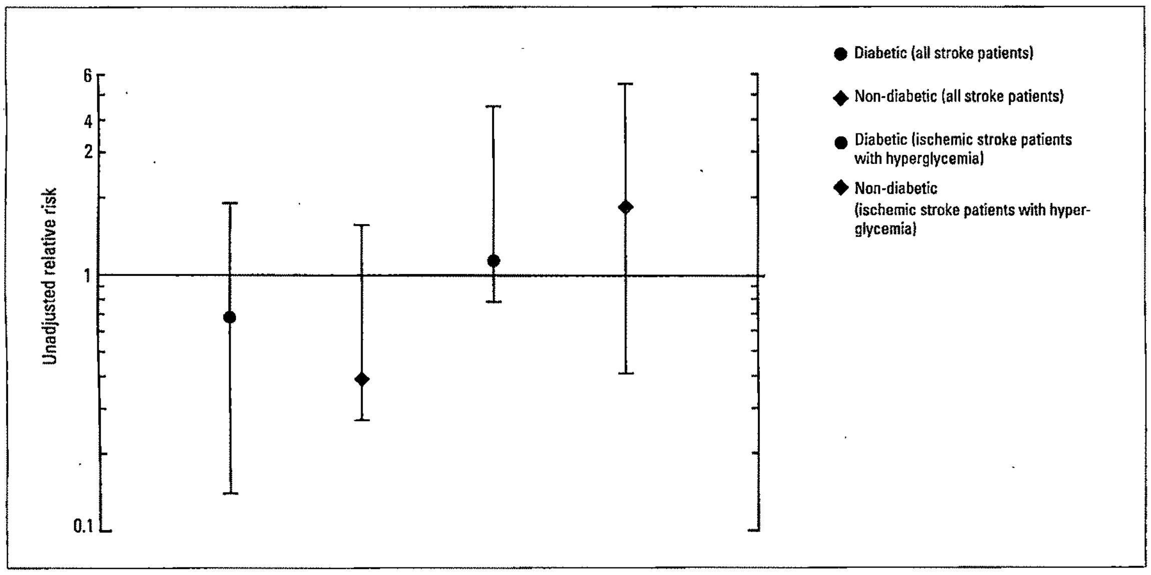

Figure 1. Unadjusted relative risk of in-hospital mortality within 30 days.

adjusted relative risk of in-hospital mortality within 30 days in ischemic stroke patients with MBGL >6.1-8.0 mmol/L (121-144 mg/dL) at admission and after 72 hours was 1.83 (95% CI, 0.41-5.5) for non-diabetic patients and 1.13 (95% CI, 0.78-4.5) for diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 higher relative risk of in-hospital 30-day mortality than diabetic patients.

DISCUSSION

There are multiple mechanisms of the neuronal damage and blood-brain dysfunction in patients with prolonged stress hyperglycemia. Elevated blood glucose is common in the early phase of stroke and is probably mediated by the increased release of the "stress hormones"–cortisol and epinephrine.

Relative insulin deficiency associated with increased lipolysis associated with hyperglycemia diminishes cerebrovascular reactivity. Even in nondiabetic patients stress hyperglycemia may be a marker of deficient glucose regulation in individuals with insulin resistance and developing diabetes mellitus.[7] By provoking anaerobic metabolism, lactic acidosis, calcium overload, decreased mitochondrial function and free radical production, hyperglycemia may be a cause of the direct membrane lipid peroxidation and cell lysis in the zone of the numbra and penumbra, leading to the direct death of neurons and dysfunction of the blood-brain barrier and promoting hemorrhagic infarct conversion. Also, insulin resistance is a very well known indirect risk factor for stroke onset due to increased thrombophilia, endothelial dysfunction and inflammation.[8]

Progression of ischemic tissue damage is accompanied by increased glutamate secretion and decreased gamma-aminobutyric acid, mediating the spreading depression of neuronal activity.[8] There is increased activity of neuronal endonucleases and activation of the enzymes of the arachidonic acid cycle-cyclooxigenase-2 and 5-lypoxigenase in the first 24 hours. These enzymes are rate-limiting enzymes in arachidonic acid metabolism, leading to production of prostacyclin E2(PGE2) and cysteine-leukotrienes (cys-LTs), which are highly potent cerebral vasoconstrictors that lead to enhanced vascular permeability, which induces formation of vasogenic edema.[9]

Recent MRI studies have confirmed the correlation of penumbral tissue loss and elevated blood glucose levels. Using a subcutaneous glucose sensor for 72 hours of glucose monitoring, there was strong evidence of a link between infarct expansion and hyperglycemia, suggesting that hyperglycemia not only determines the initial infarct volume, but also the infarct volume enlargement.[6]

Previous clinical trials have shown that hyperglycemia at admission is correlated with a worsened clinical outcome. In non-diabetic patients stress hyperglycemia was associated with a 3-fold risk for fatal stroke at 30 days and a 1.4-fold risk for poor functional outcome as compared with normoglycemic patients.[11-14] In several thrombolysis trials, hyperglycemia has been found to be associated with decreased odds for neurological improvement and also with increased secondary hemorrhagic events, which leads to speculation that hyperglycemia might be partially responsible for the diminishing beneficial effect of rtPA and early reperfusion.[15,16]

In our study we have shown that there is an unadjusted relative risk of in-hospital mortality within 30 days of 0.68 (95% CI, 0.14-1.9) in nondiabetic patients and of 0.39 (95% CI, 0.22 -1.56) in diabetic patients. Non-diabetic patients with hyperglycemia had a 1.7 higher relative risk of in-hospital 28-day mortality than diabetic patients, which correlates with previous studies showing a relative risk about 2.0 times higher in non-diabetic patients than diabetic patients.[11-14]

All patients who died within 30 days (diabetic and non-diabetic) varied in MBGL (6.1-36 mmol/L at admission, 6.1-24 mmol/L after 72 hours), but most of them (in both groups) had an MBGL between 6.1-8.0 mmol/L (121-144 mg/dL), which confirms that it is not only important to reduce extremely high MBGL, but also to regulate the moderate hyperglycemia (similar to the results of the Glucose Insulin in Stroke Trial-GIST-UK).[12]

The results of this study are limited because relative risk was not adjusted for other risk factors but despite that, a strong and consistent association between admission and 72 hours prolonged hyperglycemia and increased 30-day stroke mortality, especially in non-diabetic patients suggests that not only high but also moderate hyperglycemia is an important risk factor affecting stroke outcome.[11-14] Our results once again demonstrate the need for systematic clinical studies to encourage the restoration of normoglycemia in the acute phase of stroke, with or without applying thrombolysis and/or neuroprotectives in both non-diabetic and diabetic patients.[15,16] The European Stroke Initiative (EUSI) and American Stroke Association (ASA) would need to reconsider their guidelines (EUSI MBGL<10mmol/L, ASA <16.63 mmol/L), so as to reduce 30-day stroke mortality and improve functional outcome.

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Age- and body mass index-dependent relationship between correction of iron deficiency anemia and insulin resistance in non-diabetic premenopausal women

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BACKGROUND: No prospective studies have evaluated the effects of correction of iron deficiency anemia on insulin resistance in non-diabetic premenopausal women. We investigated this relationship in 54 non-diabetic premenopausal women with iron deficiency anemia.

SUBJECTS AND METHODS: All patients were treated with oral iron preparations. Insulin resistance was calculated with the Homeostasis Model Assessment formula. All patients were dichotomized by the median for age and BMI to assess how the relationship between iron deficiency anemia and insulin resistance was affected by age and BMI.

RESULTS: Although the fasting glucose levels did not change meaningfully, statistically significant decreases were found in fasting insulin levels following anemia treatment both in the younger age (<40 years) (P=0.040) women and in the low BMI (<27 kg/m^2) (P=0.022) subgroups but not in the older age (≥40 years) and the high BMI (≥27 kg/m^2) subgroups. Post-treatment fasting insulin levels were positively correlated both with BMI (r=0.386, P=0.004) and post-treatment hemoglobin levels (r=0.285, P=0.036). Regression analysis revealed that the factors affecting post-treatment insulin levels were BMI (P=0.001) and post-treatment hemoglobin levels (P=0.030).

CONCLUSION: Our results show that following the correction of iron deficiency anemia, insulin levels and HOMA scores decrease in younger and lean non-diabetic premenopausal women.

It is well known that complex interactions exist among insulin, insulin resistance, iron and anemia. A mutual relationship has been identified between insulin and iron metabolism. Insulin both stimulates the synthesis of ferritin and causes a rapid and marked stimulation of iron uptake of cells by redistributing transferin receptors from the intracellular compartment of the cell membrane to the cell surface. Regulation of iron uptake by insulin occurs in parallel with its effects on glucose transport.[2] On the other hand, insulin action is also influenced by iron. Iron causes hyperinsulinemia and insulin resistance by inhibition of insulin internalization and actions.[3] In fact, the initial and most common abnormality seen in conditions with iron overload is hepatic insulin resistance.[4] In previous animal studies, it has been shown that glucose turnover increases in iron deficiency, and this increase is primarily due to enhanced peripheral insulin responsiveness.[5-8] Interestingly, there are some reports indicating that low iron status increases insulin sensitivity in lacto-ovo vegetarians. In addition, phlebotomy is followed by decreases in serum glucose as well as by improvements in both beta-cell secretion and peripheral insulin action.[9,10]

Insulin plays an important role in regulation of erythropoiesis both with its ability to boost activity of the transcription factor, hypoxia-inducible factor-1A (HIF-1A), and more directly as a growth factor influencing development of reticulocytes.[11] On the other hand, some recent reports suggest that rising hemoglobin/hematocrit (hemoglobin/hematocrit) levels are a component of insulin resistance syndrome, presumably due to the facilitative effect of insulin on erythropoietin synthesis.[12-14] Conversely, in patients with chronic renal failure, anemia has been suggested to be responsible for the insulin resistance commonly seen in these patients.[15-18]

Hyperinsulinemia and insulin resistance constitute a risk factor for atherosclerotic heart diseases.[19] It is commonly accepted that premenopausal women carry less risk for cardiovascular diseases essentially due to the protective effect of intrinsic estrogen hormone.[20] In premenopausal women, iron deficiency, which is usually caused by menstrual loss, is a very common health problem. Some animal and human studies indicate that iron deficiency increases glucose tolerance and insulin sensitivity. In that case, low iron status in premenopausal women may exert an independent and additional protective role besides hormonal status for atherosclerotic heart diseases. To the best of our knowledge, there have not been any prospective studies reporting the effects of correction of iron deficiency anemia on insulin resistance in non-diabetic premenopausal women. In this prospective study, we investigated how insulin resistance is affected by correction of anemia and how this relationship might be affected by anthropological parameters such as age and BMI.

Table 1. Pre- and post-treatment laboratory parameters of all patients.

	Pre-treatment	Post-treatment	*P*
Hemoglobin (g/dL)	9.76±1.73	13.13±1.04	<0.001
Hematocrit (%)	30.26±4.25	39.11±2.92	<0.001
Iron (µg/dL)	20.94±15.14	83.80±27.09	<0.001
Ferritin (ng/mL)	5.56±4.07	33.40±23.76	<0.001
Transferrin saturation (%)	4.77±4.00	25.94±8.85	<0.001
Glucose (mg/dL)	94.89±12.50	94.26±10.70	0.693
Insulin (µIU/mL)	9.94±6.56	7.90±3.60	0.007
HOMA score	2.40±1.80	1.86±0.91	0.009

Table 2. Pre- and post-treatment laboratory parameters of low and high BMI subgroups.

		Lean BMI	High BMI	*P*
Pre-treatment	Hemoglobin (g/dL)	9.92±1.97	9.62±1.50	0.538
	Hematocrit (%)	30.55±4.95	30.00±3.55	0.639
	Iron (µg/dL)	19.58±15.79	22.21±14.67	0.527
	Transferrin saturation (%)	4.58±3.92	4.94±4.15	0.747
	Ferritin (ng/mL)	5.25±3.36	5.83±4.67	0.613
	Fasting glucose (mg/dL)	92.15±8.52	97.43±15.08	0.123
	Insulin (µIU/mL)	9.18±7.35	10.64±5.79	0.419
	HOMA score	2.13±1.89	2.64±1.71	0.304
Post-treatment	Hemoglobin (g/dL)	13.18±1.04	13.08±1.07	0.742
	Hematocrit (%)	39.42±2.87	38.81±2.98	0.449
	Iron (µg/dL)	80..85±26.96	86.54±27.42	0.446
	Transferrin saturation (%)	24.97±7.76	26.85±9.81	0.442
	Ferritin (ng/mL)	30.05±16.21	36.38±28.87	0.338
	Fasting glucose (mg/dL)	91.85±9.31	96.50±11.56	0.111
	Insulin (µIU/mL)	6.29±2.82	9.39±3.65	0.001
	HOMA score	1.43±0.67	2.26±0.93	<0.001

SUBJECTS AND METHODS

We recruited 54 anemic premenopausal women (menstruating women of reproductive age) who had iron deficiency anemia due to menstrual loss (median age, 40 years; mean age, 36.28±10.64 years; range, 15 to 52 years) for this study. Serum ferritin values below the normal range and transferrin saturation below 15% were accepted as indicators of iron deficiency. Blood hemoglobin and hematocrit values below the normal range (≤12 g/dL and ≤35%, respectively) were accepted as indicators of anemia. All patients were treated with oral iron preparations (daily 225 mg ferroglycine sulfate), and the median duration of treatment was three months. Patients were excluded from the study if they had family histories of diabetes mellitus, repeatedly had fasting venous serum glucose levels >110 mg/dL or were previously placed on iron replacement treatments. Previous medications other than iron preparations that had already being used by the patients were continued. Informed consent was obtained from each subject after approval of the experimental protocol by the local human ethics committee. For each patient included in this study, hemoglobin, hematocrit, serum iron, transferrin saturation and serum ferritin were measured in 12-hour fasting blood both prior to the onset of iron replacement and 15 days after stopping iron treatment due to improvement of anemia. Both pre-treatment and post-treatment insulin and glucose levels were measured in three different venous serum samples taken within intervals of 5 minutes after 12 hours of fasting. Insulin level was measured with the ECLIA (E lectroChemiLuminescense ImmunoAssay) method using a Roche Modular Analytics E170 machine (Elecsys insulin kit No. 12017547). Insulin resistance (IR) was calculated according to the Homeostasis Model

Table 3. Pre- and post-treatment laboratory parameters of younger and older age subgroups.

		Younger age	Older age	*P*
Pre-treatment	Hemoglobin (g/dL)	10.08±1.80	9.49±1.66	0.217
	Hematocrit (%)	31.25±4.40	29.41±3.99	0.114
	Iron (μg/dL)	19.48±15.89	22.21±14.61	0.514
	Transferrin saturation (%)	4.47±3.98	5.02±4.08	0.621
	Ferritin (ng/mL)	5.28±3.08	5.79±4.79	0.656
	Fasting glucose (mg/dL)	95.04±11.16	94.74±13.80	0.935
	Insulin (μIU/mL)	10.27±7.20	9.65±6.08	0.734
	HOMA score	2.47±1.93	2.33±1.71	0.776
Post-treatment	Hemoglobin (g/dL)	13.18±0.87	13.08±1.19	0.717
	Hematocrit (%)	39.32±2.45	38.92±3.30	0.623
	Iron (μg/dL)	83.96±25.65	83.66±28.73	0.968
	Transferrin saturation (%)	26.24±8.84	25.69±9.01	0.824
	Ferritin (ng/mL)	27.85±12.06	37.98±29.67	0.123
	Fasting glucose (mg/dL)	91.80±10.08	96.38±10.93	0.118
	Insulin (μIU/mL)	7.55±3.02	8.20±4.07	0.516
	HOMA score	1.74±0.79	1.97±1.00	0.355

Assessment (HOMA) formula: HOMA-IR=fasting glucose (mmol/L)×fasting insulin (mU/L)/22.5.

In all patients, we searched for the existence of a possible relationship between iron deficiency anemia and insulin resistance. All patients as a whole group were dichotomized by the median for age (<40 years, n=25 and ≥ 40 years, n=29) and BMI (<27 kg/m^2, n=26 and ≥ 27 kg/m^2, n=28) to assess how this relationship, if it existed, was affected by age and BMI.

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL, USA) for Windows 10.0 programs. Results were expressed as means±standard deviation. Comparisons between pre- and post-treatment levels were made by the paired T test. Simple (Pearson) correlation coefficients between HOMA-IR and measures of variables were calculated, and a multiple linear regression analysis was performed, considering HOMA-IR as a dependent variable and all others as explanatory variables. Since the levels of HOMA-IR strictly depended on fasting insulin and glucose concentration, we did not consider these parameters in the multiple regression analysis. Results were analyzed with 95% confidence intervals and probability levels less than 0.05 were considered significant.

RESULTS

The patients included in this study had a mean BMI of 26.84±5.95 kg/m^2, a mean waist/hip ratio of 0.82±0.10 and mean age of 36.28±10.64 years. When all 54 patients were assessed as a whole, statistically significant decreases were found in fasting insulin levels and HOMA scores following the correction of iron deficiency anemia while pre-and post-treatment fasting glucose levels did not change meaningfully (Table 1). In the presence of anemia, neither fasting insulin levels nor HOMA scores were found to be significantly correlated with either hematological or iron parameters. After correction of the anemia, both fasting insulin levels and HOMA scores were found to be positively correlated with both BMI and post-treatment hemoglobin levels, with statistical significance. In the regression analysis, the factors affecting post-treatment insulin levels were found to be BMI (P=0.001) and post-treatment hemoglobin levels (P=0.030).

When all the patients were dichotomized by the median for BMI into two subgroups as low (mean BMI, 21.90±2.62; range, 17 to 26 kg/m^2) and high (mean BMI, 31.43±4,22; range, 27 to 44 kg/m^2) subgroups, the high BMI subgroup consisted of older patients than the low BMI subgroup (42.50±5.51 and 29.58±10.82 years, $P<0.001$, respectively). Neither pre-treatment nor post-treatment levels of hemoglobin, hematocrit, serum iron, transferrin saturation, serum ferritin and fasting glucose differed significantly between the high and the low BMI subgorups. Also, pre-treatment fasting insulin levels and HOMA scores in the high and low BMI subgroups did not differ significantly from each other, but the mean post-treatment fasting insulin levels and HOMA scores were found to be significantly lower in the low BMI subgroup than in the high BMI subgroup (Table 2). The fasting glucose levels of the low and high BMI subgroups did not change meaningfully following iron treatment. After correction of the anemia, both insulin levels (from 9.18±7.35 to 6.29±2.82, P=0.022) and HOMA scores (from 2.13±1.89 to 1.43±0.67, P=0.032) in the low BMI subgroup decreased significantly, whereas decreases in insulin levels (from 10.64±5.79 to 9.39±3.65, P=0.150) and HOMA scores (from 2.64±1.71 to 2.26±0.93, P=0.145) in the high BMI subgroup were less evident and statistically insignificant.

When all patients were dichotomized by the median for age into two subgroups as younger (mean age, 26.92±8.16; range, 15 to 39 years) and older (mean age

44.34±3.38; range, 40 to 52 years) age subgroups, the subjects in the older age subgroup also had a higher BMI (29.52±5.50 and 23.74±4.91 kg/m^2, $P<0.001$). Neither pre-treatment nor post-treatment levels of hemoglobin, hematocrit, serum iron, transferrin saturation, serum ferritin, fasting glucose, serum insulin and HOMA scores differed significantly between the older and younger age subgroups (Table 3). Although statistically insignificant, post-treatment fasting glucose levels in the younger age subgroup had a tendency to fall (from 95.04±11.16 to 91.80±10.08, P=0.064), whereas post-treatment fasting glucose levels showed a tendency to rise in the older age subgroup (from 94.76±13.80 to 96.38±10.93, P=0.529). Fasting insulin levels and HOMA scores in the younger age subgroup decreased significantly after iron treatment (from 10.27±7.18 to 7.55±3.02, P=0.040 and from 2.47±1.93 to 1.74±0.79, P=0.032, respectively), but the decreases in these parameters in the older age subgroup were lesser and statistically insignificant (from 9.65±6.06 to 8.20±4.07, P=0.081 and from 2.33±1.71 to 1.97±1.00, P=0.146 respectively).

DISCUSSION

The most important result of this study is that the relationship between iron deficiency anemia and insulin levels (and HOMA scores, which are accepted as indicators of insulin resistance) seen in non-diabetic premenopausal women is multi-factorial. Our results show that some anthropological parameters such as age and BMI have an influence on the relationship between iron deficiency anemia and insulin levels.

When all 54 patients were assessed as a whole, the results of this study differed from the results of animal and similar, but not identical, human studies, which reported that iron deficiency increases glucose tolerance and insulin sensitivity.[5-9] According to our results, in general, following treatment of iron deficiency anemia, insulin levels and HOMA scores in premenopausal women decreased, with statistical significance. Our results showed that the decreases in insulin levels and HOMA scores actually occurred in patients of younger age and lower BMI. However, these parameters also showed a tendency to decrease rather than to increase in patients of older age and high BMI.

To the best of our knowledge, there are no published human studies that assess the relationship between iron deficiency anemia and insulin resistance other than reports indicating that low iron status enhances insulin sensitivity in lacto-ovo vegetarians.[9] Previously reported human studies investigating the relationship between anemia and insulin resistance usually consisted of patients with diagnoses of either thalassemia[21-24] or aplastic anemia,[25] and in general, subjects with these diagnoses are considered to have simultaneous iron overload. The relationship between iron overload and insulin resistance is well known.[26] Patients with thalassemia and aplastic anemia have only the anemia factor as the common denominator with iron deficient patients, and therefore, it would be a mistake to consider these patients anemic, but at the same time iron overloaded patients are in the same category with iron deficient patients when evaluating insulin resistance. Our results also differ from the results of animal experiments showing that iron deficiency increases glucose tolerance primarily due to an increase in peripheral insulin responsiveness.[5-8] Similar studies have also been done with chronic renal failure patients in whom insulin resistance is accompanied with many other factors,[15,17,27] and anemia has been suggested as the causal factor for insulin resistance in these patients. Moreover, it has been reported that insulin resistance is reduced or improved in these patients due to either the direct effect of erythropoietin treatment or the indirect effect of anemia correction.[15,16,27] With respect to anemia, our results are similar to the results of the studies done with patients with chronic renal failure. However, our results indicate that neither low iron status itself nor the resultant anemia of iron deficiency are the causes of the higher insulin levels and HOMA scores.

In this study, the results of the subgroup analysis for age and BMI suggest that the anthropological characteristics of a study population may affect the relationship between iron deficiency anemia and insulin resistance, so the contrary results found in this study could be due to the different anthropological characteristics of the study population. The reason for the different responses in means of insulin resistance to iron treatment exerted by the younger age/low BMI and the older age/high BMI subgroups is not clear given that subjects were of the same gender and had similar hormonal status. We speculate that patients of younger age and low BMI are more energetic and active following the treatment of anemia compared to patients of older age and higher BMI, and the expenditure of more energy might be an additional factor contributing to the reduction of insulin resistance. Also, the therapy duration of three months is not long enough to see the changes in the levels of insulin and HOMA scores in patients with older age and high BMI who already have established insulin resistance when compared with patients of younger age and low BMI. The results of these subgroup analyses indicate both the necessity of taking the anthropological characteristics of the study population into account while assessing the relationship between iron deficiency and insulin resistance, and the need for further studies with different population groups.

On the other hand, there are some recent reports suggesting that the rising of hemoglobin/hematocrit values might be a component of the insulin resistance syndrome.[12-14] In this study, we also found that there were statistically significant positive correlations between post-treatment hemoglobin levels and insulin levels as well as between post-treatment hemoglobin levels and HOMA scores. Also, regression analysis revealed that the factors affecting post-treatment insulin levels were BMI and post-treatment hemoglobin levels. These results of regression and correlation analyses provide support for the existence of a relationship between insulin resistance and hematological parameters. Therefore, when considering the treatment of iron deficiency anemia, targeting lower hemoglobin/hematocrit levels may be a suitable and a necessary action for patients of older age and higher BMI who already have established insulin resistance, and particularly for the patients in whom impaired glucose tolerance accompanies iron deficiency.

We do not know the exact underlying mechanism that explains the significant decrease in fasting insulin levels and HOMA scores after the treatment of iron deficiency anemia in premenopausal women. Also, we do not know whether the decrease in insulin levels and HOMA scores following iron therapy is due to iron replacement itself or correction of the resultant anemia. Although there are some reports showing that insulin promotes the synthesis of erythropoietin by boosting the activity of HIF-1A, which functions physiologically as a detector of both hypoxia and iron-deficiency,[11] and induces the synthesis of glucose transporters as well as glycolytic enzymes, it is not known whether diminished activity of HIF-1A following iron therapy affects the synthesis and secretion of insulin or not. Such a relationship, if it exists, could be responsible for the decrease in insulin levels and HOMA scores following iron replacement, so it is clear that this topic merits further investigation.

Due to the role of insulin resistance and iron-dependent oxidative stress in the onset and progression of atherosclerosis, the relationship between iron deficiency and insulin resistance has importance. Despite some contrary reports,[28,29] it has been shown that there is a link between iron status and the pathogenesis of atherosclerosis.[30-35] Also, some evidence from previously published data show that the progression of an atherosclerotic plaque can be decelerated by reducing body iron stores with phlebotomy.[31,36] When the results of our study are assessed in this perspective, it can be concluded that iron deficiency has a reducing effect on insulin levels in patients of younger age and lower BMI in whom atherosclerosis and its complications are expected to be less prevalent, whereas such an effect was not evident in patients of older age and higher BMI in whom atherosclerosis and its complications are expected to be more prevalent. This result is not compatible with the hypothesis that low iron status in premenopausal women may play an independent and additional protective role for atherosclerotic heart diseases.

In conclusion, our results show that an age- and BMI-dependent relationship exists between iron deficiency anemia and insulin levels (and HOMA scores) in non-diabetic premenopausal women. When considering the treatment of iron deficiency anemia, targeting lower hemoglobin/hematocrit levels may be an appropriate and a necessary action for the patients of older age and higher BMI, particularly for patients in whom impaired glucose tolerance accompanies iron deficiency.

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original article

Comparison of the erythrocyte sedimentation rate measured by the Micro Test 1 Sedimentation Analyzer and the conventional Westergren method

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BACKGROUND: The erythrocyte sedimentation rate (ESR) remains the most widely used laboratory test for monitoring infections, inflammatory diseases and some types of cancer. Several test methods have been developed recently, and as a result, the safety and reliability of ESR testing procedures have improved. The purpose of this study was the comparison of two methods, the traditional manual Westergren method (reference method of the International Committee on Standardization in Hematology) and a new semiautomated technique, the Micro Test 1 for determining the ESR.

SUBJECTS AND METHODS: Blood samples were collected after a night's fasting from 200 hospitalized and ambulatory patients. Undiluted blood samples anticoagulated with K3 EDTA that had Micro Test 1 values ranging from 2-82 mm/h were used for comparison with the Westergren method.

RESULTS: Linear regression analysis comparing the Micro Test 1 and the reference method yielded satisfactory correlations and regression for samples ($r=0.910$; $P=0.0001$; $y=4.91+0.86\,x$; $Sy/x=6.85$). A Bland-Altman analysis showed no evidence of systematic bias between the Micro Test 1 and the reference method.

CONCLUSION: The Micro Test 1 system was easy to use, had a satisfactory operative practicability, required minimal maintenance, and reduced contact with potential biohazards.

The erythrocyte sedimentation rate (ESR), now more appropriately referred to as the "length of sedimentation reaction in blood (LSRB)", remains the most widely used laboratory test for monitoring infections, inflammatory diseases and some types of cancer. ESR-related methods have been used since ancient times. Its scientific basis was disclosed in the 18th century, subsequently forgotten and rediscovered in the 19th century. Fahraeus and his scholar Westergren finally popularized the method. The basic factors influencing the sedimentation rate were understood by the early decades of this century and the most satisfactory method of performing the test was introduced by Westergren in 1921. In 1988, the International Committee on Standardization in Hematology (ICSH) (Leuven, Belgium) described an ESR validation procedure as well as a method for producing ESR reference material (ICSH reference method) in the laboratory where it is to be used. The ICSH and the National Committee for Clinical Laboratory Standards (NCCLS), by using the recommended specimen, ethylenediamine tetra acetic acid tripotassium salt (K3 EDTA), which is more reliable than the traditional sodium citrate.[1,2]

ESR is a nonspecific reaction; it is a measure of the present severity of pathological processes. In general, the ESR is increased in all acute and inflammatory conditions. Variations in the ESR depend on the nature and severity of the process. One of the most important uses of the ESR is in screening for the presence of more or less occult disease and, as such, it is considered a valuable routine procedure.[3-7] The ESR still maintains its important role in the diagnosis and follow-up of rheumatoid arthritis and temporal arteritis. It is commonly used as a diagnostic or classification criterion for temporal arteritis and polymyalgia rheumatica, as a prognostic index for monitoring disease activity and for establishing remission in patients. Recently, studies indicate that ESR may be of clinical significance in sickle cell disease, osteomyelitis, and surprisingly, in non- inflammatory conditions such as stroke, coronary artery disease, and prostate cancer.[8,9]

The ESR rate measured by the Westergren method is marginally affected by age, race, and blood storage. Despite its importance in many clinical conditions, the ESR should be used only as a clinical guide to aid in the diagnosis, management, and follow-up of these different clinical situations. Hematocrit, fibrinogen concentration and fibrinogen availability (amount of fibrinogen per red blood cell) have effects on erythrocyte sedimentation. Sedimentation is increased in anemia, more so in megaloblastic than in iron-deficiency anemia, and pronounced polycythemia inhibits sedimentation. Sedimentation is also inhibited by variations in red cell shape, e.g., spherocytosis, bacantocytosis, and sickle cell formation.[10,11]

In recent decades, several new techniques for measuring ESR have been developed and introduced in clinical laboratories. The advantages of the new techniques are to guarantee safety to operators by using automated and closed systems, which automate the measurement itself and optimize the workflow and the use of human resources. The new techniques also create a unique workstation for measuring ESR and performing other hematological tests in a single specimen. We compared the Micro Test 1 semiautomated analyzer (SIRE Analytical Systems, Udine, Italy) and the Westergren erythrocyte sedimentation rate method approved by the ICSH.[12]

SUBJECTS AND METHODS

In this study, subjects were randomly selected from the entire population of both hospitalized and ambulatory patients. Blood samples were obtained under standardized conditions (collection in the morning after a night's fasting) and processed for analysis during routine work. Samples were obtained from 200 patients, including 85 men and 115 women. The men were aged 51.27±15.92 (mean±SD) years, range 9-82 years; the women were aged 45.00±16.08 years, range 8-75 years. All blood samples were collected in K3 EDTA vacutainers and in sodium citrate tubes and assayed within 4 hours of venipuncture, and the blood was mixed carefully before mechanical aspiration, according to the ICSH recommendation. Undiluted blood specimens anticoagulated with K3 EDTA were used for analysis. Blood samples with Micro Test 1 ESR values ranging from 2-82 mm/h were selected for comparison studies. The reference technique was the Westergren method, which was performed according to the ICSH recommendation.

The Micro Test 1 is a semi-automated analyzer for measurement of the ESR. The contents of the tubes were mixed by slow rotation for about 3 minutes. This system employs a particular capillary where blood is moved by a special hydrodynamic system. Micro Test 1 requires only 30 microliters of blood and is optimal for pediatric use. The system uses an infrared ray microphotometer with a light wavelength of 950 nm. The electrical pulses, collected by a photodiode detector, are directly correlated to the concentration of erythrocytes present at each capillary level. The pulses, measured per time unit, are then used to delineate the sedimentation curve for each sample by means of a mathematical algorithm. The mean decrease in the signal per time unit, called medium signal, and the square root of the integral signal were transformed to comparable Westergren values by a linear regression model. Improvements were recently made to the original technique. Specifically, the rotation speed was increased from 16 to 60 rpm to achieve a better, more complete mixing of blood. The system operates at a rate of 180 samples per hour in continuous loading, providing a result about every 20 seconds.[13]

Previous studies have indicated that erythrocyte sedimentation occurs in three phases. Most models of erythrocyte sedimentation are formulated as a sigmoid function, but consider the erythrocyte sedimentation process to consist of three distinct phases: single-cell fall; fall of rouleaux and aggregates, and cell packing. Recently, a piecewise (three-phase) continuous model has been developed. The hematocrit has little influence on either the fall rate of particles in the first phase or the duration of the first phase. This is also true for fibrinogen availability and for fibrinogen concentration at low hematocrit. At high hematocrits the duration of the

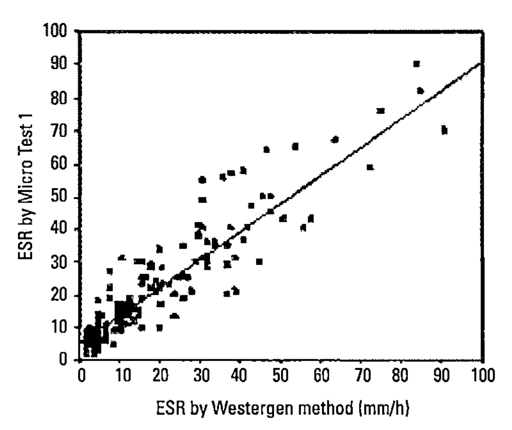

Figure 1. Comparison of the Micro Test 1 and the manual Westergren method for measuring ESR by regression analysis (r=0.910, *P*=0.0001).

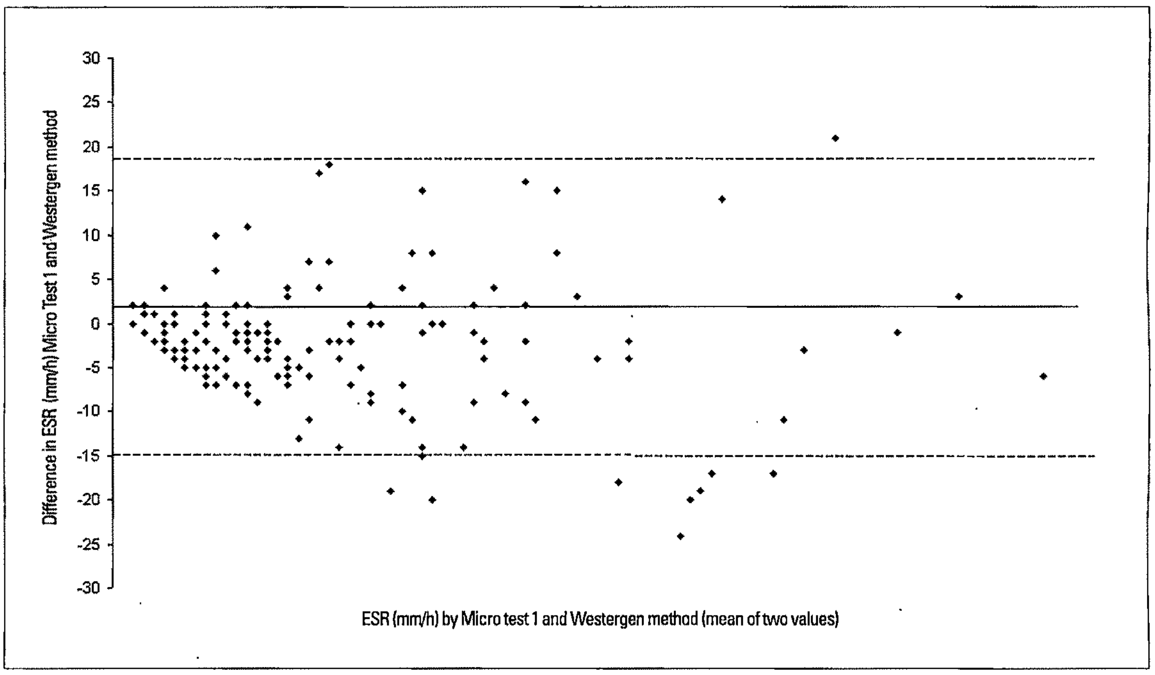

Figure 2. Bland-Altman plot of ESR values from the Micro Test 1 and the manual Westergren method.

first phase increases with fibrinogen concentration. The rate of fall of rouleaux during phase 2 and ESR both decrease exponentially with the hematocrit and increase linearly with fibrinogen concentration. While phase 2 is more closely correlated to fibrinogen availability than to fibrinogen concentration or to hematocrit, this is not the case for ESR. Thus hematocrit, fibrinogen concentration and fibrinogen availability are more important to the velocity of sedimentation in the second phase than to the sedimenting velocity during phase 1 or to the duration of phase 1.[1]

SPSS package 11.00 was used to estimate the linear regression and the correlation between Micro Test 1 and the Westergren method. We computed means and standard deviation. The data from method comparison studies were analyzed by simple least squares linear regression to obtain the y-intercept, the slope, and the SD of the regression line (Sy/x), and Pearson's correlation coefficient, and the data also were compared by the Altman-Bland analysis.[14]

RESULTS

With the MicroTest 1, the ESR was 21.10±16.56 mm/h (mean±SD); with the reference method the ESR was 18.72±17.48 mm/h. Linear regression analysis showed a satisfactory correlation between the two methods ($r=0.910$, $P=0.0001$; $r^2=0.83$; $y=4.91+0.86x$; and $Sy/x=6.85$) (Figure 1). The Bland-Altman data analysis showed no systematic bias and 95% of all samples fell into the narrow 95% limits of agreement ($d-1.96s=2.38-[2\times8.87]=-15.00$ and $d+1.96s=2.38+[2\times8.87]=+19.76$) (Figure 2).

DISCUSSION

The ESR test is one of the most common and traditional laboratory tests in the world. The method is easy to perform and inexpensive and therefore it is used as a routine test for many clinical conditions worldwide. The ESR should be used only as a clinical guide to aid the diagnosis, management, and follow-up of these different clinical situations.[15] In 1988, the ICSH described an ESR validation procedure as well as a method for producing ESR reference material in the laboratory. To determine the factors affecting ESR values, correlations were analyzed between the ESR obtained by the standard Westergren method for red blood cell concentration, haematocrit, and plasma proteins including fibrinogen, albumin and globulins.The ESR has some disadvantages since it requires a large volume of sodium citrate and at least 1 hour of testing time.[16] In this context, several kinds of simple, rapid and safe methods have been developed. These methods offer the advantages of speed, safety, and uniform specimen handling. Systems utilizing sedimentation columns less than 200 mm in length may be less sensitive to changes at higher ESR than the Westergren method. In our study, Micro Test 1 results correlated satisfactorially with the ICSH recommended method. The Bland-Altman analysis showed no evidence of a systematic bias between the Micro Test 1 and the reference method. The mean difference that we found of 2.38 in our study is nearly the same with the studies performed with Micro Test 1.[17] This difference can be explained with higher values measured with Micro Test 1 at elevated ESR values (>25 mm/h).

In our comparison of Micro Test 1 and the standard method of Westergren, good agreement was obtained. The Micro Test 1 technique produced results similar to those obtained by the Westergren method. The probability of obtaining the same results for all samples using the two different methods to measure the same parameter is unlikely, but it is possible to find the differences between the results of the new and the reference method. If this difference does not affect the interpretation, then one could use the two measurements. In addition, due to its operational characteristics it is a suitable tool for clinical laboratories with a high workload as well as for emergency laboratories. The Micro Test 1 system was easy to use, had a satisfactory operative practicability, required minimal maintenance, and reduced contact with potential biohazards.

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brief report

Smoking habits among Saudi female university students: prevalence, influencing factors and risk awareness

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Smoking is a recognized health problem worldwide.[1] Smokers are at an increased risk of developing several serious and potentially fatal diseases such as heart disease, cancer and respiratory illness.[2] Women who smoke also experience gender-specific health consequences, including various adverse reproductive outcomes.[3] The prevalence of smoking among women is consistently lower than men, especially in developing countries where there is a strong influence of culture and tradition.[4] The situation, however, is changing and the epidemic of smoking among women in the developing world is increasing.[5]

Eastern Mediterranean countries, including Saudi Arabia, follow the same global trend of gender differences in smoking patterns.[6,7] Several studies conducted over the past 20 years showed that the tobacco epidemic is firmly established in the Kingdom of Saudi Arabia.[8,9,10] However, most of studies were conducted in males, limited to cigarette smoking and confined to the central region.

The aims of this study were to assess the prevalence and patterns of smoking among Saudi female students at King Abdulaziz University in Jeddah city, Western Region and to determine factors influencing student smoking behavior and their knowledge about its adverse health effects.

METHODS

This was a cross-sectional study conducted by distributing a self-administered questionnaire to a sample of 1100 female students attending the colleges of Medicine, Dentistry and Arts and Science. The questionnaire was a modification of the Arabic version of the Global Health Professionals Survey and the Global Youth Tobacco Survey core questionnaire.[7,11] The questionnaire was designed to gather data on demographics, prevalence of tobacco use, smoking-related knowledge and attitudes, smoking cessation, exposure to second hand smoke and knowledge about health effects of tobacco use.

The questionnaire was distributed to the students by one of the researchers, who explained the purpose of the study and content of the questionnaire. Anonymity of participants was emphasized, therefore no name or student serial number was requested. Confidentiality was strictly maintained with all completed questionnaires.

All data management and analysis was done using the SPSS statistical program (version 10).The percentage of smokers among different demographic groups was compared using Chi-square test. A logistic regression analysis was used to examine the independent effect of variables that were significant in the bivariate analysis controlling for age.

RESULTS

A total of 1050 students completed and returned the questionnaire (95.5% response rate). Approximately 20% of the respondents were dental students, 36% medical students and 44% arts and science students. Ages ranged between 18 to 26 years.

The prevalence of smoking in relation to demographic characteristics of the study sample is displayed in Table 1. Among respondents, 11% were current smokers. Among the smokers, 5% were cigarettes smokers, 8.7% were users of the water pipe (i.e. museal, shisha) and other tobacco products and 2.7% were smokers of both cigarettes and other tobacco products. When comparing the prevalence of smoking based on college, age or GPA (grade point average) no statistically significant differences were found, whereas a significantly higher smoking prevalence was associated with a higher family income level ($P<0.05$), although it did not retain its significance in the multivariate logistic regression.

Smokers were significantly more likely to have a parent or a friend who smokes. Multivariate logistic regression analysis showed that having a parent or a friend who smoke was independently associated with smoking. Students who had a close friend or a parent who smokes were respectively, 5 (OR= 5.2; $P<0.01$) and 2 (OR= 2.3; $P<0.01$) times, more likely to be smokers independent of age and level of income.

Knowledge about smoking hazards among students is presented in Table 2. Regarding smoking in general, the majority of students (95.4%) were aware of the habit being hazardous to their health. A higher percentage of smokers (12%) than nonsmokers (2.7%) thought smoking was not hazardous to their health ($P<0.001$). Regarding smoking other forms of tobacco (including shisha and museal), 22% of students thought they were less harmful than cigarettes and the difference between smokers (37%) and nonsmokers (21%) was also significant ($P<0.001$).

Knowledge about the association between smoking and adverse health effects varied among respondents (Table 2). For instance, more than 90% of students were aware of the association between smoking and heart disease, yet only 75% were aware of its association with stroke. There was no statistically significant difference between smokers and nonsmokers in their knowledge about the health consequences of smoking, except for hypertension. However, there were statistically significant differences between students from different colleges in their knowledge about the adverse health effects of smoking.

Table 1. Prevalence of tobacco use according to demographic characteristics of the study sample

Demographic Data	Number (N)*	Percentage (%)	Smoking Prevalence (%)
Total sample	1050	100	11
Age			
< 20	519	49.4	11.4
21-23	482	45.9	9.8
> 24	49	4.7	18.4
College			
Medicine	379	36.1	8.5
Dentistry	205	19.6	11.7
Arts & Science	464	44.3	12.7
GPA			
Excellent	266	25.6	11.7
Very good	492	47.4	10
Good	231	22.3	10.4
Satisfactory	49	4.7	20.4
Income†			
< 5000	230	23.3	8.7
5000- 10,000	209	21.2	9.1
10,000- 20,000	286	29	10.8
> 20,000	261	26.5	16.5
Parents§			
Smokers	377	36.2	17[§]
Non-smokers	665	63.8	7.5
Friends§			
Smokers	231	22.1	28.1[§]
Non-smokers	812	77.9	6

*Numbers do not add up due to missing data †$P<0.05$ §$P<0.001$

DISCUSSION

This was a cross-sectional study conducted to determine the spread of the tobacco epidemic among female university students in Jeddah in the Western Region of Saudi Arabia. In our study, 11% of students were current tobacco users, which is consistent with several international studies.[6,12] The results are also consistent with a study conducted on female college students in Saudi Arabia in which a prevalence of 8.3% was reported.[10]

Water pipe and forms of tobacco other than cigarettes were the most commonly used (8.7%) among our study population. There is growing evidence that tobacco use other than cigarettes is spreading across all world regions.[6,7] In the Eastern Mediterranean Region, water pipe smoking is enjoying a great rise in popularity and becoming a behavioral norm, especially for women.[13] There is a paucity of epidemiological data regarding water pipe use in Saudi Arabia. A recent study in male medical college students in Riyadh showed a higher proportion of water pipe users 44% than cigarette users 32.3% among smokers.[8]

Water pipe smoking is perceived by many as being less dangerous than cigarettes.[13,14] The same misconception was found in our study, where 23% of students and 37% of smokers thought other forms of tobacco use (including water pipe) were less harmful than cigarettes. Although data regarding the content hazard and health effects of water pipe use is not well established, there is growing evidence of the adverse health consequences of water pipe use, pointing towards it being as harmful as cigarettes if not even more.[13] This calls for

Table 2. Knowledge of smoking adverse health effects among students

Smoking Hazards	% of students unaware of smoking adverse health effects				
	Total Sample	Smoking Status		College	
		Smokers	Non-smokers	Medical & Dental	Arts & Science
Smoking harmful	4.6	12.2*	2.7	2.9	4.7
Forms of tobacco other than cigarettes harmful	22	37.2*	20.9	24.2	20.5
Heart disease	2	1.8	2	1.9	2
Lung cancer	0.6	0	0.7	0.3	0.9
Oral cancer	6.9	10.8	6.4	5.3	9*
Other cancers	16.6	18.3	16.4	14.6	19.4*
Hypertension	16	25.9	14.7*	12.9	19.9*
Stroke	25	30.5	24.4	23.4	27.2
Sexual dysfunction	35	39.3	34.3	37.2	31.8
Impotence	44.2	44.8	44.1	46.9	40.6*
Gum disease	5	7.3	14.7	4.9	5.1

*$P<0.05$

public health strategies to control this potential major health problem, including carrying out further epidemiological and toxicological research and health education.

Our results indicated that both parental and peer smoking were important predictors of smoking. The social influence of parents and peers are important determinants of smoking that are well supported in the literature.[15] These results indicate that smoking prevention programs should take a future family-focused direction and address peer pressure as one of the most important factors which motivate adolescents to smoke.

Although a high level of awareness and a good amount of knowledge about the health consequences of smoking was present among the students, it did not affect their smoking behavior. A simple relationship between risk awareness and smoking behavior should not be expected. A recent study on perceptions about cigarette smoking and risks among college students stated that young people, including college students, tend to undervalue the health consequences associated with smoking.[16] Informing the public, especially such a highly educated and influential group, about the health consequences of smoking remains the back bone of health education. However, better health knowledge alone cannot stem the smoking epidemic especially since the habit develops in adolescents when long term risk may be of little concern and seen as being far in the future. Tobacco control efforts targeting young adults need to emphasize that each cigarette smoked is doing their body harm.

In conclusion, although most of the respondents were aware of the health consequences of smoking, the habit was not uncommon amongst them. The higher rate of water pipe use and the perception that it is less harmful than cigarettes points at an emerging public health problem. More research is necessary to expand our understanding of smoking habits, factors influencing initiation and persistence among females. In addition, collaborative and more comprehensive anti-tobacco efforts are important to curb the tobacco epidemic in Saudi Arabia.

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case report

Spontaneous regression of a herniated cervical disc

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Since its first description by Key in 1945, spontaneous regression of herniated disc material was described by other authors at different levels of the spine, especially in the lumbar slab.[1-3] However, very few cases of spontaneous resolution of cervical disc herniation have been reported in the literature.[4-7] Most cases are confined to disc herniation associated with radiculopathy.[5] We report a particular case of spontaneous resorption of symptomatic cervical disc herniation without surgical treatment.

CASE

Our patient was a 48-year-old sportsman, operated on in 1988 for a thyroid nodule, who presented at our institution for a sudden severe pain on the left C6 level. He described acute cervical pain and paresthesia in his left upper limb. There was no history of trauma. His neurological examination revealed no motor or sensory deficits. All reflexes were brisk and symmetric. The basic x-rays of the cervical spine showed no particular signs. Whereas MRI showed a large disc herniation at the C5-C6 level, that was eccentric to the left side and which encroached the subarachnoid space and the left C6 root. The other intervertebral spaces were normal (Figure 1). We recommended that the patient undergo an anterior discectomy. However, the patient refused the operation because of his history of thyroid surgery. He then received analgesics, non-steroidal anti-inflammatory drugs and a muscle relaxant during four weeks with immobilization by cervical collar. In the meantime, he reported spectacular improvement of his symptoms. Three months later, the follow-up MRI showed a complete regression of the extruded disc (Figure 2).

DISCUSSION

The spontaneous resolution of herniated lumbar discs

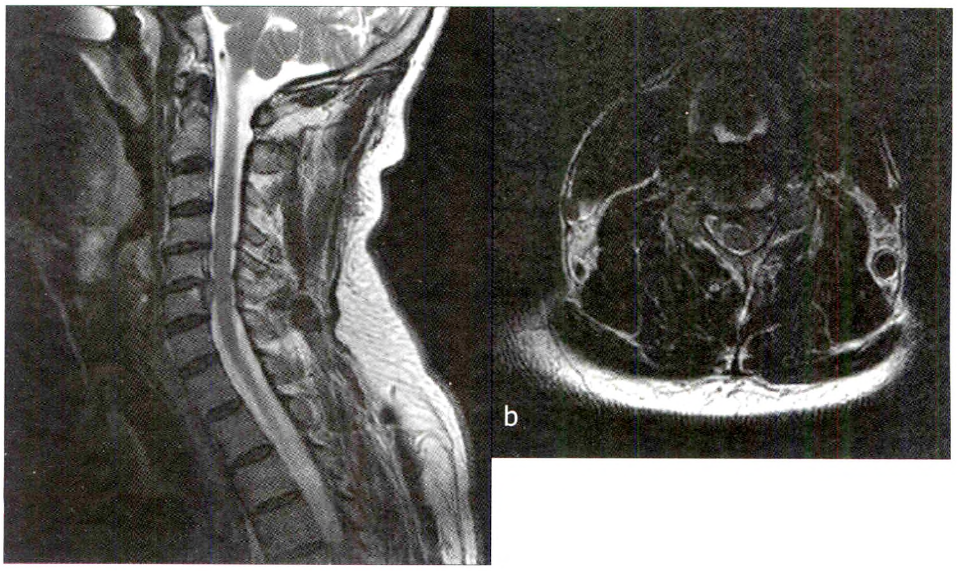

Figure 1. Magnetic resonance images in sagittal (a) and axial (b) T2-weighted views revealing large C5-C6 disc extrusion, through a disruption of the anulus fibrosus, eccentric to the left side and compressing the anterior aspect of the spinal cord.

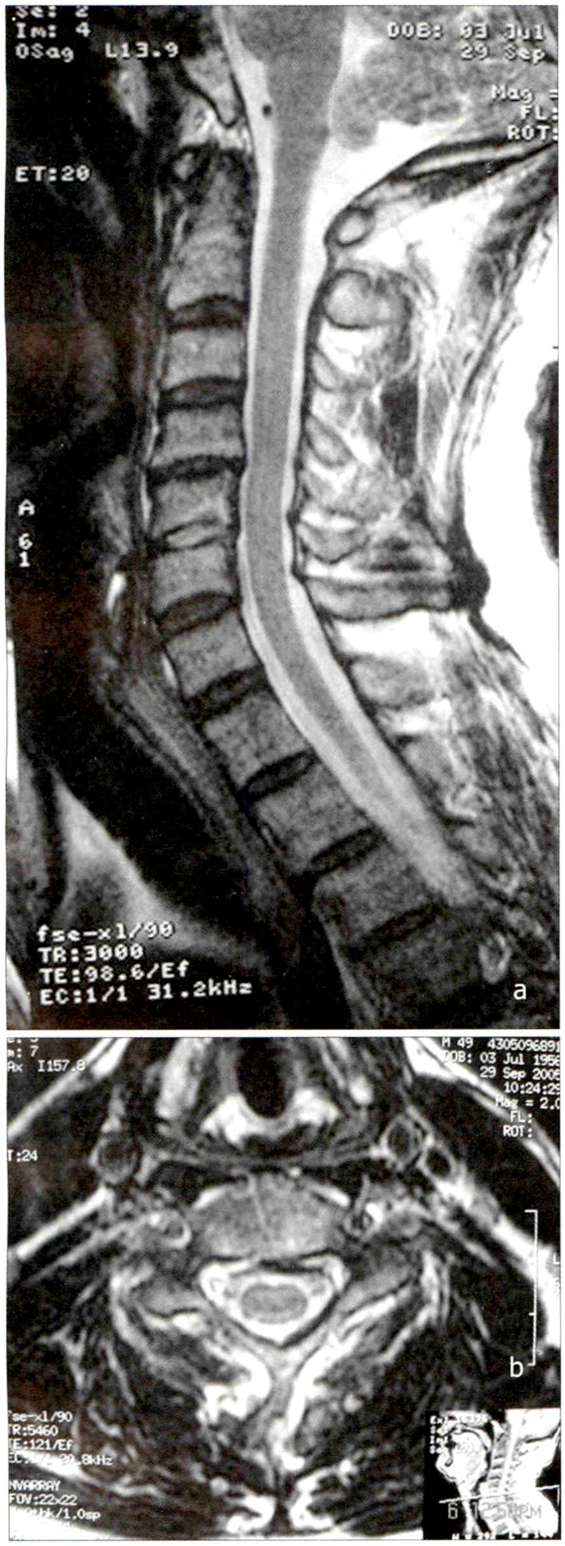

Figure 2. Follow-up MRI in sagittal (a) and axial (b) T2-weighted images showing that the herniated disc completely varnished.

is a well-established phenomenon.[3,8-11] Thus, the disappearance of disc compression has been reported occasionally in the cervical spine[7,12] and rarely in the thoracic region.[13] Most cases of disappearing herniation of the cervical disc reported in the literature were diagnosed using computed tomography. Only 40 or so cases were followed using MRI.[4-6,10,13-15]

Cervical disc herniation typically manifests with radiculopathy caused by compression of the cervical root and/or myelopathy due to spinal cord compression. Radiographic studies would allow the final diagnosis, and show evidences of the magnitude and level of the herniation. In neurosurgical practice, most surgeons that have documented cervical disc extrusion using MRI, support surgical treatment of patients with intractable radiculopathy and/or cervical myelopathy. The operation for cervical disc disease is a relatively safe procedure and surgical management might have resulted in more rapid and complete improvement of symptoms.[5] Nevertheless, the potential tendency of regression of the disc herniation has suggested that many cervical discs could be successfully managed without any surgical care.[7,12,16,17] Maigne et al[17] reported a decreasing size or disappearing herniated cervical soft-disc in 20 of 21 patients with cervical radiculopathy followed by computed tomography. In agreement with the reported approach, our case demonstrated extrusion of the nucleus pulposus through a disruption of the anulus fibrosus and posterior longitudinal ligament (Figure 1b). Furthermore, this regression tendency is based on the anatomic position of the extruded disc material.[4,14] Since cervical disc herniation was classified as migration-type on sagittal view and lateral-type on axial view, it exhibited frequently a regression, and our case corroborates this condition. Moreover, Matsumoto et al showed in a recent retrospective study of conservatively treated patients with cervical myelopathy caused by cervical soft disc herniation[14] that the type and level of herniation on MRI have prognostic value. They concluded that patients with median-type herniations on axial images and those with herniations at more rostral intervertebral levels obtained favorable outcomes after conservative treatment.

Herniated disc regression detected on MR images might show expanded dehydration of the pulposus nucleus and resorption of hematoma, which subsequently occur after anulus rupture.[17] In an experimental study performed on rabbits, Minamide et al[18] demonstrated that the proteoglycan chains of the herniated fragments undergo autolysis with loss of their hydrophilic capacity. Some reports have studied the mechanism and factors affecting such regression. It has been suggested that once herniated disc material is exposed to the vascular environment of the epidural space, the herniated fragment is then treated as a foreign body undergoing inflammatory reaction, neovascularization and phagocytosis, yielding a decreasing size of this fragment.[6]

To hope for a spontaneous resorption of symptomatic cervical disc herniation, opting for a non-surgical treatment is a very courageous choice. It which should be established on good symptomatic analysis of MRI findings. This kind of decision should be case-based taking into account the high potential risk of neurological deterioration.

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case report

Cryptosporidiosis in a renal transplant patient treated with paromomycin

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Cryptosporidium is an intracellular protozoan parasite and one of the most commonly reported enteric pathogens in both immunocompetent and immunocompromized hosts worldwide. It causes an infection resulting in diarrhea and biliary tract disease[1] and is now recognized as a major cause of diarrhea in both immunosuppressed and immunocompetent hosts. The risk of severe and or prolonged disease is high in immunocompromized patients including solid organ transplantation recipients. It is more commonly seen in countries with increasing population and poor sanitary conditions. Prevalence is much higher in human immunodeficiency virus (HIV)-infected patients.[2] The treatment of cryptosporidiosis in immunosuppressed patients is still not clearly defined and response to proposed therapies is suboptimal.

CASE

A 60-year-old woman who received a living-related renal transplant 4 months earlier, presented with a 5-day history of colicky abdominal pain and watery diarrhea 6-7 times per day. There was no vomiting, fever, or other constitutional symptoms. Her immunosuppressant regimen included tacrolimus 2 mg twice daily, prednisolone 10 mg once daily, and co-trimoxazole DS once daily. Other medications included mycostastin Suspension and omeprazole.

On examination she was fully oriented and afebrile with a blood pressure of 70/40 mm Hg. Her abdomen was soft and lax, with mild tenderness in the epigastrium, left flank and sluggish bowl sounds. The remainder of her physical examination was unremarkable. She was started on intravenous fluid resuscitation with a normal saline bolus.

Lab results showed a normal complete blood count, urea 22 mmol/L, creatinine 351 umol/L, potassium 4.1 mEq/L, and sodium 132 mEq/L. Blood and stool cultures were negative. Stool for *Clostridium difficile* toxin was negative. Colonoscopy with multiple biopsies from transverse, descending and rectosigmoidal colon were taken, and all showed the heavy presence of cryptosporidium on PAS stain (Figure 1). Esophageogastroduodenoscopy was normal. Biopsies taken from the esophagus, stomach and duodenum showed no evidence of parasite, granuloma or inclusion bodies.

She was started on paromomycin 500 mg twice daily and loperamide. Her condition gradually improved, and her creatinine normalized with intravenous hydration. She was discharged after four days of admission on paromomycin 500 mg orally three times dailty for 1 month in addition to her previous anti-rejection regimen. On follow-up visits, her diarrhea had completely stopped. One month after discontinuing paromomycin she had her regular bowel movement while her immunosuppressant was the same as before her hospitalization. Her serum creatinine was 73 μmol/L and her trough tacrolimus level was 6.6 μmol/L.

DISCUSSION

Cryptosporidiosis is a protozoal infection, which has been increasingly recognized as a cause of diarrheal illness in both immunocompetent and immunocompromised hosts. The risk of severe and prolonged disease is more in patients with cellular and humoral immune deficiencies including HIV-infected population, organ transplant recipients, patients on immunosuppressant drugs, patients with IgA deficiency or hypogammaglobunemia.[3]The frequency of isolating *Cryptosporidium* from stool of renal transplant patients was significantly higher than that found in two control groups, one consisting of patients with end-stage renal disease on hemodialysis and the other consisting of patients with hypertension without renal abnormalities.[15] Infection is more common in countries with poor sani-

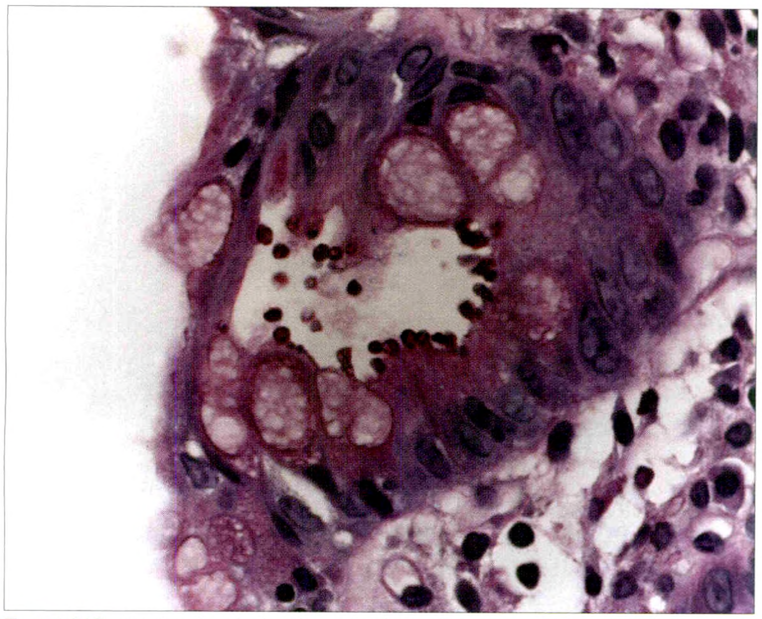

Figure 1. PAS stained section of colon biopsy showing positive organisms in the glandular lumen (100X, PAS Stain).

tary conditions and increased crowding. Although more frequent in children less than 2 years of age, outbreaks occur worldwide in all age groups.[4,5] Since early 1980s, massive outbreaks have been linked to municipal drinking water supplied in different parts of the world, especially Europe and North America.[6]

Twenty-four species of *Cryptosporidium* have been identified. *Cryptosporidium parvum* is the only species responsible for clinical disease in humans, but it is not host specific, since it also infects other mammals.[7] Its transmission is via spreading from infected person or animal or fecally contaminated environmental source, such as food or water.[8] Pathogenesis is not well understood, and no toxin has been identified. It causes secretary diarrhea, and the intracellular nature of the infection interferes with absorption of gut secretions. The organism can spread via intestinal lumen to involve biliary system where they can cause strictures and cholangitis.

Diagnosis is usually established by identification of the organism in stool, duodenal aspirate or biopsy specimen. Since cryptosporidia spores are not detected by routine examination of the stool for ova and cyst, special stains are used such as Modified Acid Fast Stain. Fluorescent assays have been used to increase the sensitivity compared to light microscopy.[9,10] Enzyme immunoassay (EIA) kits are also available. Acid fast stain has a sensitivity of 94% and a specificity of 76% and EIA has a sensitivity and specificity of 100% compared to direct immunofluorescence.[11] Serological detection using indirect fluorescent-antibody (IFA) assay or ELISA is also available. In our case, stool examination for parasite was negative but biopsies from the colon were positive.

There is no reliable therapy for cryptosporidiosis. Recovery usually depends on immune status of the host. Non-specific therapies are often given to immunodeficient patients including anti-diarrheal and supportive care with enteral or parenteral nutrition. A number of specific therapies have been tried. The largest experience is with paromomycin in acquired immune deficiency syndrome (AIDS) patients, where it was not found to be more effective than placebo.[12] In AIDS patients, the best treatment is improvement of the immune status with Highly Active Antiretroviral Therapy, which can help resolve cryptosporidium infection.

In renal transplant patients, no data are available on the best modality to treat this infection. Reduction of immunosuppressive therapy alone was reported to be associated with cure of *Cryptosporidium*-induced sclerosing cholangitis.[13] Our patient responded well to paromomycin combined with an anti-motility agent. Establishing a definite role for paromomycin in treating cryptosporidium infections in renal transplant patients needs a well-designed clinical trial. This is the first case report of the use of paromomycin in the treatment of *Cryptosporidium* in a renal transplant patient.

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case report

Bilateral benign endobronchial schwannomas

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Neurofibroma and neurilemmoma are rare tumors of neurogenic origin that may present at any age. Neurilemmoma, also known as schwannoma, is even more uncommon.[1] It typically arises from neural crest cells that encapsulate the nerve sheath and can originate anywhere in the thorax commonly from sympathetic or intercostals nerves, and rarely from the vagal nerves.[2] Localization of schwannomas in the bronchi or within the pulmonary parenchyma is also very rare.[3] Here, we report a case of multiple endobronchial schwannomas with bilateral proximal airway involvement.

CASE

An 80-year-old man was admitted to our hospital with complaints of pleuritic chest pain and dyspnea on exertion which started two months previously. He denied smoking cigarettes, but stated that the walls in his house were plastered with white-stucco, including environmental asbestos minerals. He had no previous history of neurogenic lesions elsewhere. The past and family histories were also unremarkable for neurofibromatosis. Chest examination revealed fine crackles on the left lung fields and breathing sounds were diminished at the left posterior lung base. Chest X-ray showed a linear density on the right side, extending from the hilar region to the pleural surface, with an irregular mass lesion in the hilar region, moderate pleural effusion on the left side, and the syndrome of Chiliaditi. The patient was not cooperative for pulmonary function tests and his arterial blood gases were within normal limits. In addition to chest X-ray, a thorax CT revealed an irregular soft-tissue density with punctuate calcification surrounding and narrowing the left upper lobe bronchus, and left pleural thickening with moderate pleural effusion (Figure 1). Bronchoscopic examination showed mucosal fragility, engorgement and narrowing of the right upper lobe bronchus and nearly complete obliteration of the left upper lobe bronchus with a submucosal tumor. Although the lesions had smooth surfaces, the mucosal biopsies were taken from each one. The histopathological examination of each of these biopsies revealed that the tumors were placed under the bronchial epithelium, and composed of fascicles of spindle cells and palisading nuclei without pleomorphism and mitotic activity (Figure 2). The immunohistochemical staining of tumor cells were strongly positive for S-100 protein (Figure 2), and negative for collagen IV, SMA, Desmin and C-kit. CD34 immunoreactivity was detected in scattered cells. According to these findings the pathological diagnosis was reported as bilateral benign peripheral nerve sheath tumor consistent with schwannoma. The therapeutic options for endobronchial schwannomas such as surgery, electrocoagulation or Nd-YAG laser were refused by the patient. A diagnostic thoracentesis and pleural needle biopsy revealed tuberculous pleurisy. Combined antituberculous treatment of isoniazid, rifampicin, ethambutol and pyrazinamide was started. In the follow-

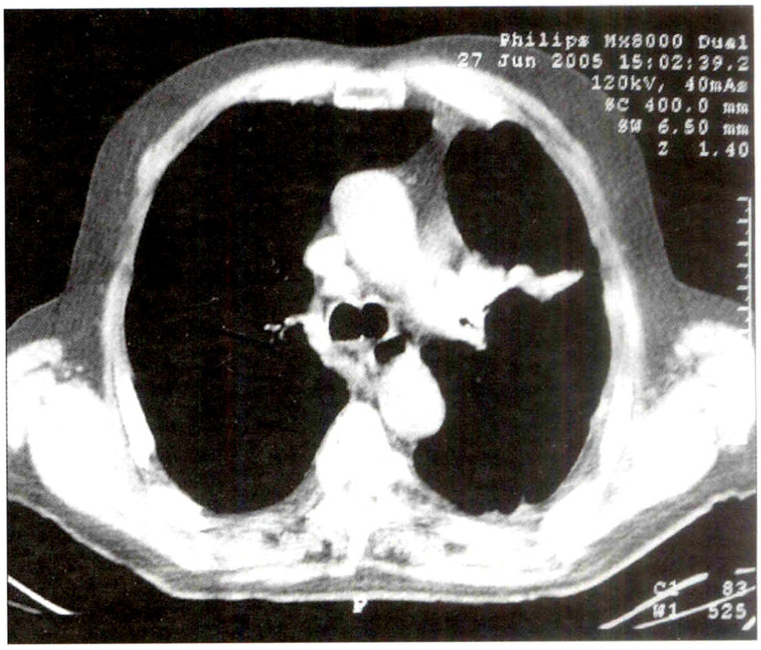

Figure 1. Thorax CT scan showing a soft tissue density obstructing left upper lobe bronchus and segmental atelectasis distal to the density.

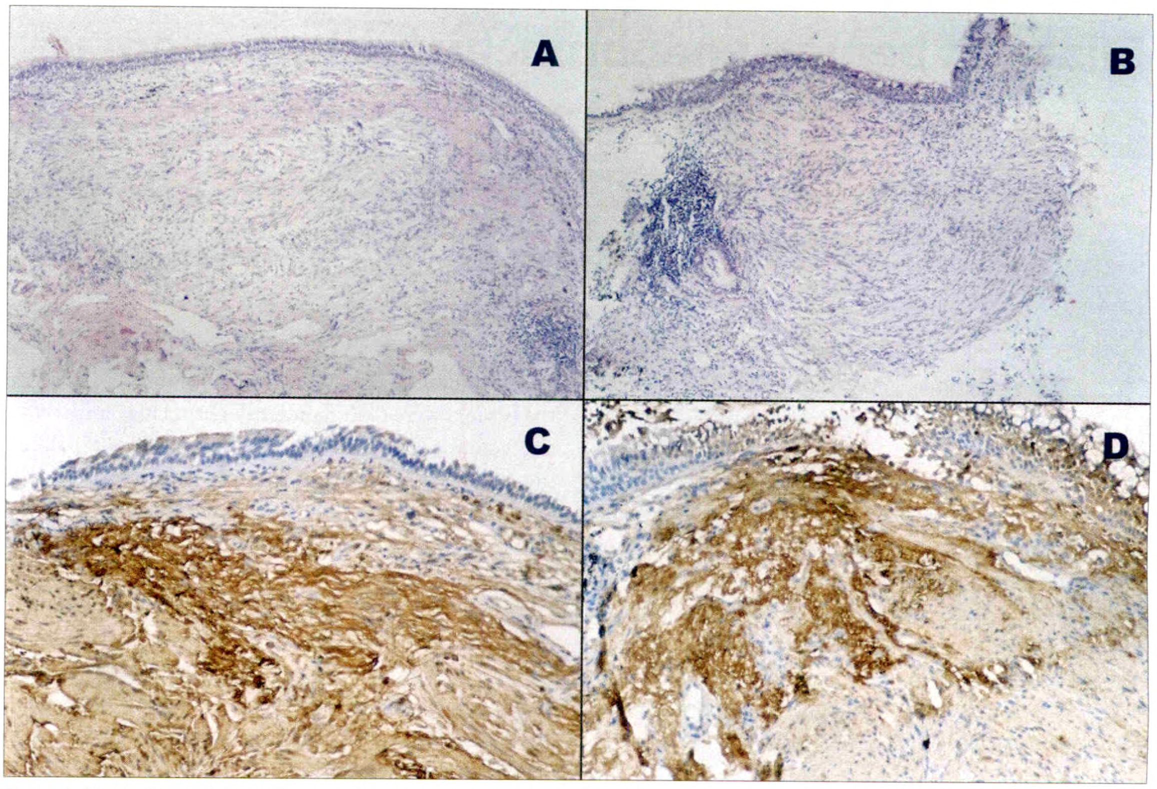

Figure 2. Bilateral bronchial biopsy specimens from right (A,C) and left (B,D) upper lober bronchus. Fascicles of spindle cells and palisading nuclei are seen under the normal mucosa (HE×40) (A,B). Immunohistochemical staining with S-100 protein revealing strongly stained tumor cells (DAB×100) (C,D).

up period, the symptoms of the patient diminished on the second month of antituberculous treatment.

DISCUSSION

Neurogenic benign tumors arising from the tracheobronchial tree are relatively rare.[4-7] Benign lung tumors have been reported to account for 1.9 % of total lung tumors and most of them are papilloma (29%), hamartoma (24%) and angioma (10%).[8] The incidence of intrapulmonary neurogenic tumors was stated as 0.2% in a series of 1664 primary pulmonary tumors.[3] Most intrapulmonary neurogenic tumors were neurofibromas, with schwannomas accounting for 25% of the tumors.[9]

Histopathological examination of the biopsy specimens in our case showed no malignant markers such as pleomorphism, atypia or mitotic activity, but schwannomas can demonstrate a degree of cellular pleomorphism and even show a degree of mitotic activity due to a reaction to degenerative change referred as ancient change. The negative staining for collagen IV, although it may be positive around Schwann cells, and the strong diffuse staining for S-100 protein reinforced the diagnosis of schwannoma.

Kasahara et al reviewed 50 cases of pulmonary neurilemmomas reported in Japan and classified them according to their localization as central and peripheral type.[10] Of these 50 cases; 25 were classified as central type (13 at trachea, 12 at bronchus). In our case, the tumors were localized in the upper lobe orifices bilaterally. Two types of tumor extension were described by Kasahara et al, one of them was intraluminal growth and the other was the combined type involving both intraluminal and extraluminal spaces. Bronchoscopic examination and CT findings showed that the tumor extension in our case was of the combined type. To the best of our knowledge, there are only two case reports of endobronchial schwannoma located at two different sites. One of them was reported in the Japanese literature in which the tumors were detected bilaterally by bronchoscopy.[11] The other was reported in the English literature in which the tumors were located in the right middle/lower lobe bronchi and in the right basalis anterior/basalis lateralis segmental bronchi.[12] In our case, the tumor nearly completely obliterated the left upper lobe bronchus and the other one was located at the bifurcation of right upper lobe bronchus.

The main symptoms of patients with endobronchial schwannoma are dyspnea, wheezing, cough, sputum production, and hemoptysis.[3-5,10] Of the cases reported by Kasahara et al, three patients with the central type and all patients with the peripheral type were asymptomatic.[6] It seems that the symptoms of our case (pleuritic chest pain and dyspnea on effort) were also not due to endobronchial tumors as the symptoms resolved after antituberculous treatment. The existence of a relationship between smoking and neurilemmoma is still unproven. Harada et al speculated that multiple endobronchial schwannomas might be caused by the proliferation of Schwann cells resulting from cigarette smoking followed by inflammation of the bronchial mucosa.[12] The presence of smoking history in all patients (three current and one former smoker) reported by Suzuki et al supported this speculation.[13] In contrast to these observations, our case denied active or passive cigarette exposure. Accordingly, there are similar cases in the pediatric age group.[1,14] The relationship between the underlying diseases and schwannoma is also unclear. In this context, newly diagnosed tuberculous pleurisy and a history of environmental asbestos exposure were present in our patient.

It is difficult to distinguish schwannoma from early bronchogenic carcinoma solely on the basis of bronchoscopic findings.[13] All bronchoscopic findings in our case were similar to bronchogenic carcinoma apart from bilateral placement of the tumors. Although it is a rare condition, the finding of multiple synchronous lung carcinomas bilaterally during bronchoscopic examination is possible. Endobronchial schwannomas are seen as nodules covered with normal bronchial mucosa bulging into the tracheobronchial lumen or raising the bronchial mucosa with hypervascularity at the spur of the bronchus.[15,16] In our case bronchoscopic examination was compatible with the latter condition.

Treatment approaches for benign lung schwannomas vary. Interventional bronchoscopic techniques (resection by forceps, electrocoagulation, Nd-YAG laser, laser ablation) and surgical resection such as lobectomy or pneumonectomy are the therapeutic options for benign schwannomas.[8,10,14,17] Although our patient had nearly complete obstruction of left upper lobe bronchus and atelectasis distal to the obstruction, he was not given treatment since he refused all treatment modalities.

The pathological examination is the cornerstone in the diagnosis of schwannoma, and bronchoscopic examination is recommended for both the diagnosis and treatment. Benign endobronchial schwannomas must be kept in mind in the differential diagnosis of the patient with multiple bronchial tumors.

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case report

Recurrent hemoptysis from diffuse tracheal nodularity due to tracheobronchopathia osteochondroplastica

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Tracheobronchopathia osteochondroplastica (TO) is a benign disease, first described in 1855 and rather rarely since. Only a few hundred cases have been reported. Osseocartilaginous submucosal nodules projecting into the lumen of the trachea and bronchi characterize the disease.[1] The mechanism of its occurrence remains controversial. Most cases are asymptomatic and frequently diagnosed incidentally during intubation, endoscopy or autopsy.[2,3] The incidence of TO appears to be underestimated in the literature in view of the fact that it is usually benign. However, a more accurate estimate of its true prevalence may become available through the use of bronchoscopy and computerized tomographic scanning.

CASE

A 66-year-old non-smoking male patient was referred to respiratory medicine at King Hussein Medical Center, Amman in July 2005 with a 6-year history of recurrent attacks of mild hemoptysis. He was assessed by different general practitioners over the years and had been diagnosed as having recurrent attacks of acute bronchitis. Several chest X-rays were done during this period, which had been reported as normal. Two weeks prior to his admission he had a mild fever sensation with excessive sweats, mainly at night. He had diabetes mellitus for 15 years and was on an oral hypoglycemic agent, which was shifted to insulin in 2002 because of poor control. Past surgical history was positive for an appendectomy 10 years ago and surgical repair of a diaphragmatic hernia 3 years later with no endotracheal intubation problems or any postoperative pulmonary complications. He was a retired phosphate mine guard but had never been in close contact with phosphate. There was no history of cigarette smoking or contacts with domestic animals or birds. There was no history to suggest contact with any case of tuberculosis. Upon admission he had a temperature of 38°C, a pulse of 80 beats/minute and a respiratory rate of 16/minute His chest auscultations revealed only a few scattered expiratory wheezes. A chest X-ray showed a left lower zone homogenous opacity obscuring the left cardiac border. Laboratory tests including a complete blood count, liver and kidney functions, and arterial blood gases were normal. Pulmonary function tests including a flow volume loop and diffusion tests were normal. His sputum cytology was negative for both malignant cells and acid-fast bacilli stain and culture. A high-resolution chest CT scan demonstrated small nodules with calcifications at the trachea wall with mild tracheal narrowing but without any deformity (Figure 1). A diagnostic fiber optic bronchoscopy showed multiple yellow-white, hard, papilla-like numerous nodules on the anterior and lateral walls of the trachea sparing its membranous part extending from just below the vocal cords to the proximal part of both main bronchi (Figure 2). Histopathological examination of the biopsy samples from these lesions showed osteocartilaginous tissue, typical of TO (Figure 3). Bronchial wash stains for bacteria, TB and fungi were negative. During his stay he was seen by an ophthalmologist and an ENT surgeon in order to rule out signs of systemic diseases, moderate diabetic retinal changes were the only abnormalities demonstrated. He was treated as a case of chest infection and had a very good clinical recovery with resolution of his chest X-ray inflammatory changes. On his 6-week follow up visit the patient showed no symptoms of chest infection but continued to complain from recurrent attacks of mild hemoptysis. His sputum and bronchial washings TB cultures that were requested during his stay in hospital proved to be negative.

DISCUSSION

Tracheopathia osteochondroplastica is an uncommon abnormality of the cartilaginous tracheal wall, charac-

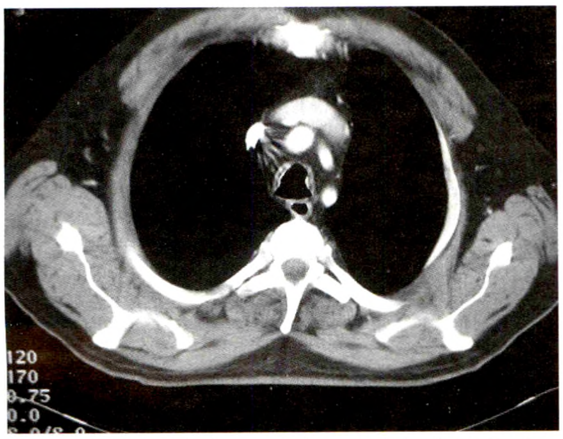

Figure 1. A computerized tomography scan of the chest showing nodules and calcifications of the trachea.

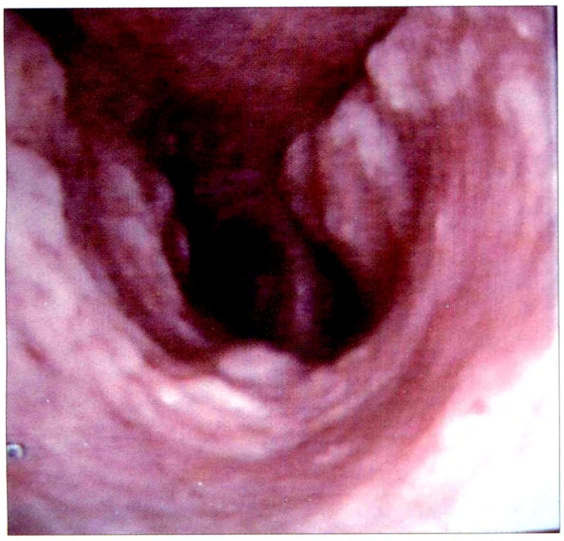

Figure 2. Fiber optic bronchoscopy showing multiple hard numerous nodules on the anterior and lateral walls of the trachea.

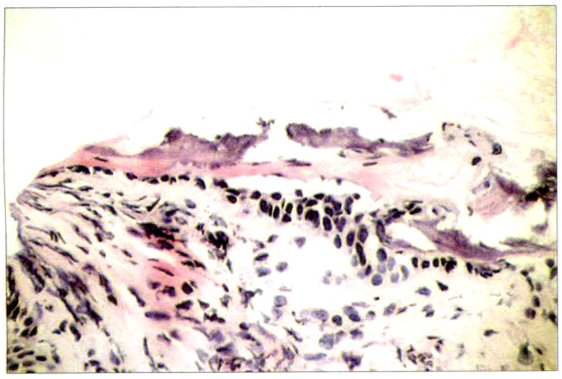

Figure 3. Microscopic examination of bronchial biopsy sample showing the abnormal osteocartilaginous tissue.

terized by the presence of osteocartilaginous calcified nodules within the submucosa, with a variable degree of diffuse tracheal narrowing. It is characterized by the presence of polyps in the trachea and main bronchi, which consist of osseous tissue. Involvement may extend to lobar or segmental bronchi. The nodules originate in the airway cartilages and thus typically spare the posterior membranous wall of the airways. The disorder is more common in men and the diagnosis is usually made in the fourth through sixth decades of life. There is no relationship to smoking or other systemic disorders. During the last sixteen-year of bronchoscopic experience at KHMC, our pulmonologists encountered only this patient with TO among more than 5000 performed bronchoscopies. This case presentation emphasizes the importance of bronchoscopic examination in the diagnosis of such cases and clearly underlines the significance of the early referral of all cases with recurrent hemoptysis to a pulmonologist.

The etiology of TO remains unknown. There are reported cases of TO with a concomitant silicosis and non-Hodgkin pulmonary lymphoma[4,5] but it seems that these cases occurred by coincidence. Our patient worked in a phosphate mine for a long period but his work did not involve direct or close contact with the raw silica. His radiological and pulmonary function tests did not suggest such a clinical diagnosis. The majority of patients remain asymptomatic, but a small number develop severe airway stenosis. Other pulmonary symptoms include dyspnea and hemoptysis. One of the complications is the increased incidence of recurrent respiratory infections. The pulmonary symptoms and complications are the consequence of narrowing and thickening of the airway walls. Our patient had described several chest infective episodes most probably because of the mucosal wall irregularity that he had. A long-standing diabetes history probably had an influence on the recurrences of these attacks. Plain chest X-ray films are often unremarkable but may demonstrate atelectasis, consolidation, tracheal modularity, or narrowing. CT reveals tracheal modularity with calcification and narrowing.[6,7] The diagnosis is usually made on the basis of endoscopy. Differential diagnosis of nodular excrescences includes tracheobronchial amyloidosis, endobronchial sarcoidosis, calcificating lesions of tuberculosis, papilomatosis, tracheobronchial calcinosis and relapsing polychondritis. Our patient didn't have any of the systemic symptoms that usually point out to the above diagnoses nor he had their histopathological finding on his bronchial biopsy, which was rather diagnostic of TO. Bronchoscopy is the most definitive diagnostic test. The bronchoscopic appearance alone is diagnostic of the disease. Although there is no specific therapy for this disorder, management of TO includes bronchodilators, prompt treatment of pulmonary infections, and bronchoscopic dilatation when indicated. However, in severe cases, bronchoscopic removal of obstructing excrescences and surgery has been performed with therapeutic effect.[8] Treatments attempted included cryotherapy, laser excision, external beam irradiation, and bronchoscopic removal of the obstructing lesions. The prognosis is usually favorable. Clinicians should include this disease in the list of differential diagnoses when confronted with symptoms like persistent and often productive cough, haemoptysis, dyspnoea and wheeze. Awareness of the condition as a differential diagnosis to neoplasm is important, to avoid unnecessary intervention or treatment.

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what's your diagnosis?

A 37-year-old married woman with 3-month history of galactorrhoea and irregular menstrual cycle

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A 37-year-old married woman presented to the gynecology outpatient department with 3 months history of galactorrhoea and irregular menstrual cycle. No history of visual problems could be elicited. After initial evaluation she was referred to the endocrinology department for further investigation of her hormonal status. The visual field examination revealed bitemporal hemianopsia on perimetry. Galactorrhoea was also observed. Her pertinent laboratory investigations included high serum calcium (14 mg/dL), high levels of serum prolactin (120 μg/L) and parathyroid hormone (110mEq/L).The thyroid stimulating hormone (TSH), cortisol, gonadotropins and serum calcitriol levels were normal. Two months later the patient presented with polyuria, polydipsia and bone pain. A high-resolution contrast-enhanced MRI (CEMRI) of the sella (Figure 1) and plain radiograph of the hands (Figure 2) was performed.

What are the abnormal findings on the MRI and the hand x-ray?

What additional studies are needed to make a diagnosis?

What is the likely diagnosis?

Answer on page: 388

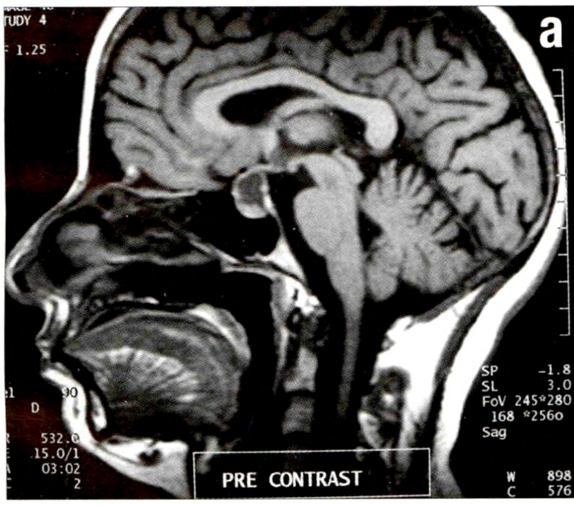

Figure 1a. T1W MRI sagittal section showing a sellar mass with hypointense center.

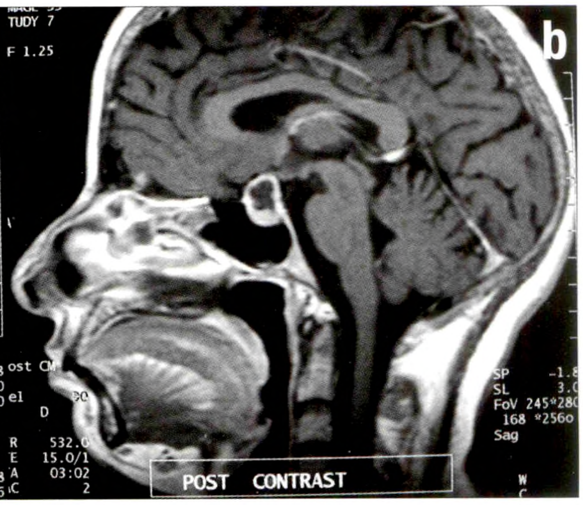

Figure 1b. Peripheral rim enhancement is seen on post-gadolinium T1W sagittal image.

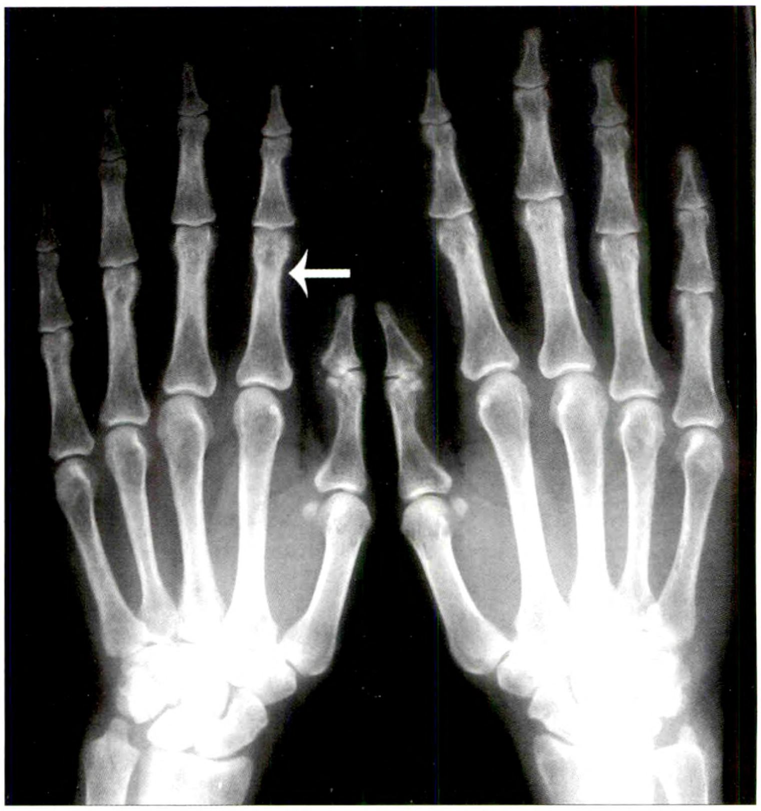

Figure 2. X-ray of the hands showing osteopenia and subperiosteal erosion in the phalanges (arrow).

Lung Cancer in Bahrain (1952-2004)

To the Editor: We read with interest the paper on 'The incidence of lung cancer in the Gulf Cooperation Council countries" by Al-Hamdan et al.[1] We are particularly concerned about the number of Bahraini patients with lung cancer included in this paper from the Gulf Centre for Cancer Registration. As such, we wish to provide a short critique of the paper and contribute additional data from Bahrain.

Applying the same WHO criteria as those used by Al-Hamdan, we reviewed all the histopathology and hematopathology archives from all government and private hospitals and clinics in Bahrain between 1952 and 2004. During these 52 years, there were 7336 Bahraini patients with malignant neoplasia, 3972 males and 3364 females (Table 1). There were 541 (7.4%) patients with primary lung cancer; 427 (79%) male, 114 (21%) females and sex ratio of 3.7:1. Primary lung cancer ranked 2nd and 11th most common cancer in the males and females respectively. It also accounted for 10.8% and 3.4% of all malignancies in the males and females respectively. Breast cancer was the most common primary malignancy in the general and female cancer population.

In Al-Hamdan, based on 1998-2001 data, there were 204 Bahraini patients with lung cancer; 151 males, 53 females and sex ratio of 2.8:1. Lung cancer ranked first and second most common cancer in Bahraini males and females respectively. It also accounted for 20% and 12.1% of all malignancies in the male and females cancer patients respectively. However, during the same period (1998-2001) we found only 54 (47 males and 7 females) patients in the pathology registries and not 204 patients as cited by Al-Hamdan.[1] This deficit of 150 raises two main questions.

Firstly, the exact origin of the additional 150 Bahraini patients must be questioned. It is quite possible that we may have missed a few cases from the pathology registries, but it is highly unlikely that we missed as many as 150. There are a number of possible explanations for this discrepancy: (a) The Bahrain data included lung cancer patients diagnosed before 1998 or after 2001. But this would put the Bahrain figure outside the standardized inclusion criteria of the period under study, thus doubting the comparative results of the entire report. (b) There is inflation of the Bahrain figures by including cases unaccounted for. We found 49 non-Bahraini patients in the pathology registries diagnosed between 1952-2004 and another 13 patients diagnosed between 1967-1998 as metastatic tumours and malignancies of unknown behaviour whether primary or metastatic (i.e. ICD-O behavioural codes B/6 and B/9 respectively). However, even if these 62 patients are added it would still not account for the 150 patient deficit. (c) There are technical errors of cancer registration such as counting multiple biopsies or cytology aspirates obtained from the same lesion and same patient according to their number. (d) The data may have included histologicaly unconfirmed but clinically diagnosed cases. But the analysis of the histological pattern of lung cancer provided is against this assumption.

Second, in view of the sampling ambiguities any interpretation of data related to Bahrain would send the wrong messages about the frequency, rank, ASR, gender distribution, sex ratio, and histological pattern of cancer patients in general and those of lung in particular. We

Table 1: The main results on lung cancer in Bahrain between 1998-2001 by Al-Hamdan from Gulf Centre for Cancer Registration as compared those of the same period and between 1952-2004 from pathology registries in Bahrain.

Differences		Al-Hamdan et al[1] 1998-2001	Bahrain 1998-2001	Bahrain 1952-2004
All Cancers	Total		1234	7336
	Males		588	3972
	Females		646	3364
Lung Cancer	Total	204	54	541
	Males	151	47	427
	Females	53	7	114
Sex Ratio		2.8:1	6.7:1	3.7:1
Rank in Males		1	4	2
% in Males		20.0	9.2	11.3
Rank in Females		2	14	11
% in Females		6.8	0.6	1.6
ASR	All population			6.2
	Males	34.3		10.4
	Females	12.1		2.6

ASR= Age Standardised Incidence Rate /100,000.

equally question the population data used in the calculation of the standardized rates as these may either be wrong or non-representative of Bahrain or other Arabian Gulf states. We also note the following: (a) The 34.3 and 12.1 age standardized rate (ASR) of lung cancer for males and females in Bahrain cited, by Al-Hamdan are not only higher than those of other populous Arabian Gulf states but would put the tiny 405 667 population of Bahrain on par with rates in Europe, North America, Japan, China, Australasia and Southeast Asia.[2,3] We feel the 10.4 and 2.6 ASR reported in this communication for males and females respectively, are more realistic and representative of the incidence of lung cancer in Bahrain. They are also consistent with data from other Gulf states.[4-6] (b) There is no adequate explanation for the higher rates of lung cancer in Bahrain in Al-Hamdan as compared to those of the nearby Arabian Gulf countries, which share many common family, genetic, environmental and socioeconomic factors. Smoking cannot be the sole factor. Otherwise, it would mean that one in every 5 persons in Bahrain will develop lung cancer during their lifetime. Furthermore, while we do not doubt the association of smoking and lung cancer, we note that all support data used in the Al-Hamdan et al paper are indirect and refer to the prevalence of smoking in the Arabian Gulf countries. It would have been more meaningful if the authors obtained direct information about smoking among lung cancer patients themselves and correlated this with the anatomical distribution and the histology of the tumours. These gaps imply that the returned cancer notification forms for cancer registration were primarily deficient in fundamental data. (c) The frequency of breast cancer as the most common cancer in Bahrain and in many other Arabian Gulf counties must not be ignored.[2,4,6]

There are 11 names on the authorship list of Al-Hamdan et al paper of whom at least 6 are registrars of their local cancer registries.[1] This raises an ethical issue of authorship. Thus while we stress that the validity of published data of any cancer registry is determined by the amount of histopathology confirmation of the cases, we note that in Al-Hamdan study, the effort of the entire behind the scene workforce including histopathologists, who contributed significantly towards its publication, was ignored and not even acknowledged. The international standard of biomedical journals is clearly against this form of authorship unless "contributorship" is acknowledged.[7,8] We need to stress that the possession of data contributed by others and the administrative affiliation of the "contributorship" are not criteria for authorship.[7,8]

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Ibn Al-Nafis: Discoverer of the Pulmonary Circulation

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The Arab physician Ala' al-Din ibn Abi al-Hazm, well known as Ibn al-Nafis, was born in the year 1210 in al-Qurashiyya, a village near Damascus, hence he was known as Al-Dimashqi. His family originally came from Qarash, a village beyond the River Oxus, and that, according to some authors, gave him the "nisbah" of al-Qurashi.[1]

His initial medical studies were in Damascus at the Great Nuri Hospital, Al-Bimaristan Al-Nuri Al-Kabir, built by the Turkish Prince Nur al-Din Mahmoud ibn Zanki after his conquest of Damascus in 1154. Ibn al-Nafis teacher at that hospital was Muhadhdhab al-Din Abd al-Rhim ibn Ali Al-Dakhwar, who established al-Dakhwariyya Medical School in Damascus, and was the Chief of Physicians for Syria and Egypt during the rule of the Ayyubid ruler al-Adil. Al-Dakhwar was appointed by al-Adil's successor, al-Muazzam, as the head of the Nuri Hospital.[2] Other contemporaries of Ibn al-Nafis were Ibn Abi Usaybi'a and Ibn al-Quff.

In 1236, Ibn al-Nafis moved to Egypt. He became Chief of Physicians *(Ra'is Al-Atibba')* in Egypt and the private physician for the Mamluk ruler Sultan Al-Zahir Baybars al-Bunduqdari, who ruled Egypt during the period 1260-1277. He had a thriving practice and became wealthy. He built a house in Cairo, and entertained rulers, leading physicians and colleagues. Towards the end of his life, Ibn al-Nafis donated his house and library to the newly established Al Mansouri Hospital, which was built in 1284 by the Mamluk Sultan al-Mansur Sayf al-Din Qalawun al-Alfi.[1-3] He died in Cairo on December 17, 1288, at the age of 78, after an unknown illness.

In addition to his medical studies, Ibn al-Nafis learnt Islamic religious law, and became a renowned expert on Shafi'i school of jurisprudence (*Fiqh*). He lectured at al-Masruriyya School in Cairo. His name was included in a book on "Great Classes of Shafi'i Scholars (*Tabaqat al-Shafi'iyyin al-Kubra*) by Taj al-Din al-Subki indicating his fame in religious law.[1]

Ibn al-Nafis was a prolific author. He had an outstanding memory and had written his books from memory without reference to other textbooks or compendia. According to Nagmia, his works can be divided into several categories[2]:

I. Original contributions:

- *Kitab Al-Shamil fi al-Sina'a al-Tibbiyya (Comprehensive Book on the Art of Medicine).* He wrote this book when he was in his thirties. It consisted of 300 volumes of notes, 80 of which were published. This book contained a section on surgical techniques, thus shedding lights on Ibn al-Nafis as a surgeon. According to Iskandar, there are three stages for each Operation: *al-I'ta'* (The presentation for diagnosis); *al-'amal* (the operative procedure); and *al-hifz* (preservation-post operative care).[1]
- *Kitab Al-Mukhtar Min al-Aghdiyah (Book of Selection of Nutrients).*
- *Al Muhadhab fi al-Kohl (The Polished Book on Ophthalmology).*
- *Bughyat al-Talibin wa Hujjat al-Mutatabbibin (Reference Book for Physicians).*
- *Kitab Jame' Al-Daqai'q fi al tibb (The Composite of Details in Medicine).*

II. Commentaries on Greek works

- *Sharh Fusul Al Buqrat (Commentary on Hippocratic Aphorism).*
- *Ibidimiya li Buqrat wa tafsiruhu li al Amrad al Wafideh (Commentary on the Epidemiology of Disease by Hippocrates)*
- *Sharh Taqdimat Al-Ma'rifah (Commentary on Hippocratic Prognostics).*
- *Sharh Tabi'at al-Insan li Buqrat (Commentary on Hippocrates book "De Natura Hominis' or Nature of Man).*

III. Commentaries on Islamic medical works;

- *Kitab Mujaz al-Qanun (Commentary on Al Qanun fi al Tibb by Ibn Sina)*. This commentary made Ibn Al Nafis most famous, and was published several times. A review of this book was written by Kahya from a copy in Turkey.[4]
- *Sharh Tashrih Al Qanun (Commentary on the Anatomy in Al-Qanun)*. In this book, he gives the earliest description of the pulmonary circulation.
- *Sharh Mufrada Al Qanun (Commentary on Simple Medicines in Al Qanun)*.
- *Sharh Masai'l Hunain (Commentary on Questions of Hunain Ibn Ishaq)*.

VI. Contributions to Islamic theology and philosophy:

- *Al Risalah Al Kamaliyyah fi al Sira al Nabawiyyah* known also as Fadil bin Natiq on the life story of the prophet of Islam.
- *Al Mukhtasar fi Ilm Usoul al Hadith (A Short Account of the Methodology of Hadith)*.

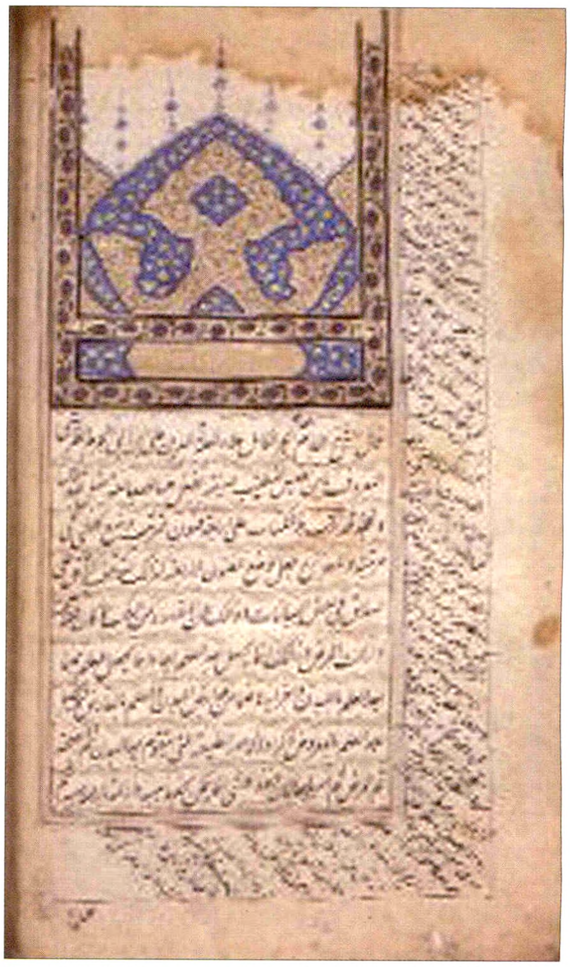
Several articles by Arab and Western authors discuss the role of Ibn al-Nafis in the discovery of the pulmonary circulation.[5-10] He challenged the Galenic concept of circulation which stated that blood reaching the right side of the heart went through invisible pores in the septum of the left side of the heart, where it mixes with air to create spirit and then was distributed to the body.[6]

Western writers gave credit of the discovery of the pulmonary circulation to Michael Servetus (1511-1553), a Spanish physician and theologist,[11] and to William Harvey.[12] Soubani and Khan elaborated on the European descriptions of circulation and the resemblance between the writings of Ibn al-Nafis on this issue and those of later European writers such as Servetus, and Colombo.[6]

Some authors believe that Western writers used Ibn al-Nafis concept of circulation in their "re-discovery" three hundred years later.[13] One writer raised questions regarding whether Ibn al-Nafis was known to the European scholars during the age of Renaissance and that they opted to ignore his writing or not give proper credit to him.[14]

The credit for recognizing Ibn al-Nafis as the discoverer of the pulmonary circulation goes to Dr. Muhyi al-Din al-Tatawi of Egypt. In 1924, Dr. al-Tatawi found a manuscript of "Sharh Tashrih al-Qanun" in the Prussian State Library in Berlin (Manuscript 912), while working on his dissertation for a doctorate at the Faculty of Medicine of the Albert Ludwigs University in Freiburg, Germany.[2,5-7] Ibn al-Nafis stated the following regarding the pulmonary circulation:

"...This is the right cavity of the two cavities of the heart. When the blood in this cavity has become thin, it must be transferred into the left cavity where the pneuma is generated. But there is no passage between these two cavities, the substance of the heart there being impermeable. It neither contains a visible passage, or as some people thought, nor does it contain an invisible passage which would permit the passage of blood, as Galen thought. The pores of the heart there are compact and the substance of the heart is thick. It must, therefore, be that when the blood has become thin, it is passed into the arterial vein (pulmonary artery) to the lung, in order to be dispersed inside the substance of the lung, and to mix with the air. The finest parts of the blood are then strained, passing into the venous artery (pulmonary vein) reaching the left of two cavities of the heart, after mixing with the air and becoming fit for the



Ibn Al-Nafis' 13th century treatise The Concise Book (*Kitab Mujiz*) which epitomized the Canon of Ibn Sina.

generation of pneuma..."[1]

In describing the anatomy of the lungs, Ibn al-Nafis stated, "The lungs are composed of parts, one of which is the bronchi, the second, the branches of the arteria venosa and the third, the branches of the vena arteriosa, all of them connected by loose porous flesh". The need of the lungs for the vena arteriosa is to transport to it the blood that has been thinned and warmed in the heart, so that what seeps through the pores of the branches of this vessel into the alveoli of the lungs may mix with what there is of air therein and combine with it, the resultant composite becoming fit to be spirit when this mixing takes place in the left cavity of the heart. The mixture is carried to the left cavity by the arteria venosa.[9]

Ibn al-Nafis also postulated that the nutrition of the heart is extracted from the small vessels passing through its wall. He stated "...Again his (Avicenna's) statement that the blood that is in the right side is to nourish the heart is not true at all, for the nourishment to the heart is from the blood that goes through the vessels that permeate the body of the heart...". This rarely mentioned contribution of Ibn al-Nafis on the nutrition of the heart and its blood supply made him the first to put forward the concept of coronary circulation.[6]

Ibn al-Nafis' works were translated to Latin in Venice, Italy, by Andrea Alpago of Belluno in 1547. He was a physician working for the Consulate of the Venice in Damascus. Few years later, Michael Servetus from Aragon, Spain, described the pulmonary circulation in his theological book, "*Christianismi Restitutio*", in 1553 and wrote, "...air mixed with blood is sent from the lungs to the heart through the arterial vein; therefore, the mixture is made in the lungs. The bright color is given to the sanguine spirit by the lungs, not by the heart."[6] The Church accused Servetus of heresy for his insistence on denying the dogma of the Trinity, and for opposing the teachings of Galen. He was burnt at the stake by order of the protestant Geneva governing council as a heretic.

About the same time, Andreas Vesalius, the famous Flemish anatomist, described the pulmonary circulation in his book "*De Humani Corporis Fabrica*", in a manner similar to Ibn Nafis' description. In the first edition of the book (1543), Vesalius agreed with Galen that the blood "... soaks plentifully through the septum from the right ventricle into the left..." However, in the second edition (1555) he omitted the above statement and wrote instead "...I still do not see how even the smallest quantity of blood can be transfused through the substance of the septum from the right ventricle to the left..." It is not clear whether Vesalius had access to Ibn al-Nafis translated work or not.

William Harvey wrote in his book "*Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*", published in 1628, about the movement of the blood and the importance of valves in the circulation of blood.[12] In his book he described the movement of the blood from the heart to the lung. However, he did not elaborate on the physiology of the pulmonary circulation and its role in the exchange of gases.[6]

We conclude that Ibn al-Nafis should be recognized as the first discoverer of the pulmonary circulation, 300 years before it was described by European physicians.

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what's your diagnosis?

Diagnosis: Multiple endocrine neoplasia type 1 (MEN 1), also known as Wermer's syndrome

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MRI revealed a soft tissue mass in the sella causing its expansion. The mass was hypointense on T1W images (Figure1a) showing peripheral enhancement on post gadolinium image (Figure 1b). A plain radiograph of the hands shows osteopenia with subperiosteal erosion in the phalanges (Figure 2). A diagnosis of pituitary macroadenoma was suggested based on the MR appearance. She was put on bromocriptine therapy following which her periods became regular. In view of subperiosteal erosion seen on the plain radiograph, a suspicion of hyperparathyroidism was made as subperiosteal erosion of the bone, particularly along the radial aspect of the middle phalanx of middle and index finger, which is virtually pathognomonic for hyperparathyroidism although osteopenia can be found in other conditions, viz. osteomalacia, multiple myeloma. Contrast enhanced CT scan of neck was performed, which revealed enlarged right inferior parathyroid gland. MRI of the abdomen was also performed which revealed a small well defined space occupying lesion in the proximal body of pancreas, which was uniformly hypointense on T1W image and hyperintense on T2W image (Figure 3a, 3b). Bilateral adrenal hyperplasia was also noted. Based on the clinical profile, laboratory findings and imaging appearance, a diagnosis of MEN 1 syndrome was suggested. She underwent trans-sphenoidal decompression of the mass and histopathology confirmed the diagnosis of pituitary adenoma. The patient also underwent total parathyroidectomy, enucleation of the pancreatic tumor. Histopathology of the resected specimens showed parathyroid hyperplasia and neuroendocrine tumor of the pancreas. She is on clinical follow up and is doing well.

DISCUSSION

Multiple endocrine neoplasia type 1 (MEN 1) also known as Wermer's syndrome, is an autosomal dominant genetic syndrome characterized by a predisposition of simultaneous or successive development of neoplasia

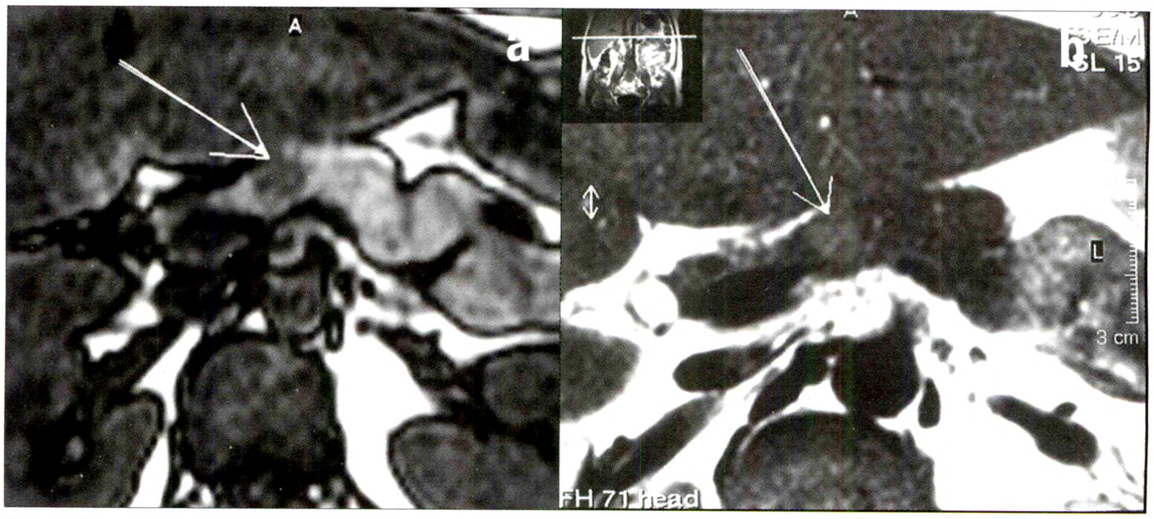

Figure 3. T1 weighted axial MR image showing a hypointense lesion in the proximal body of the pancreas (arrow) (a).The lesion appears mildly hyperintense on TSE T2 weighted axial image (arrow) (b).

and or hyperplasia of several endocrine glands.[1] It is caused by a germ line mutation in the MEN 1 gene locus coding for a tumor suppressor protein, called menin.[2] Jacob Erdheim in 1903 first described this condition in a patient with tumors involving two endocrine organs, the pituitary gland and the parathyroid glands and almost six decades later Steiner et al introduced the term "Multiple Endocrine Neoplasia" to describe a combination of tumors of three different types of endocrine glands viz. familial parathyroid, pituitary and pancreatic islet cell tumors (MEN type 1), familial pheochromocytoma, medullary thyroid carcinoma and hyperparathyroidism (MEN type 2) and non familial parathyroid tumors and papillary thyroid carcinomas (MEN type 3).[3] Classical MEN 1 includes primary hyperparathyroidism (HPT), enteropancreatic neuroendocrine tumors (EPNET) and pituitary adenomas.[4]

Primary hyperparathyroidism is the most common manifestation of MEN 1 syndrome and most of the affected individuals develop hypercalcemia by age 40. Parathyroid hyperplasia is the most common cause of hyperparathyroidism in MEN 1, although single and multiple adenomas have been described.[5] Manifestations of hyperparathyroidism in MEN 1 includes nephrolithiasis, pathological fractures, gastrointestinal and musculoskeletal complaints. Enteropancreatic neuroendocrine tumors (EPNET) are the second most common manifestation of MEN 1.[1] Most frequent tumors are gastrinomas and insulinomas.[1] Early identification of EPNET is of critical importance as these tumors represent the most frequent cause of death with this syndrome.[2] Pituitary tumors occur in more than half of patients with MEN 1 and tend to be multicentric, making them difficult to resect. Prolactinomas are the most common and are diagnosed by finding serum prolactin levels >200 μg/L and can be picked up on dynamic CEMRI.[5] Clinical symptom depends on the size of the adenoma and the intensity of hormone secretion. In addition, MEN 1 carriers can have various other endocrine or non endocrine lesions like adrenal hyperplasia, thymoma, thymic and foregut carcinoids.[3]

The diagnosis of MEN 1 syndrome is established by family screening, clinical data, and appropriate hormonal assay and stimulation tests. Family history of similar disease is very important as first-degree relatives of MEN 1 patient have about 50% risk of development of the disease.[6] Imaging studies play a crucial role in identification of the target organs of lesions suspected on the basis of clinical and laboratory findings, staging of malignant lesions and search for an occult co-existing lesion to enable correct medical and or surgical treatment planning. For parathyroid lesion, high resolution ultrasonography (US) of neck preferably with a linear probe is the initial imaging modality of choice. If neck US is negative, CT, MRI or nuclear scintigraphy is indicated for demonstration of ectopic location of parathyroid in the anterior mediastinum.[1] Currently MRI is the technique of choice for evaluation of the pituitary tumors in MEN 1 patients.[1] Abdominal USG has a sensitivity of about 60% for insulinoma, and 20-30% for gastrinoma. Endoscopic ultrasonography (EUS) has improved the rate of detection of tumors in the pancreas and duodenal wall. Intraoperative USG combined with surgical palpation is another reliable method for detection of EPNET.[1] CT has overall sensitivity of 50% for the detection of pancreatic endocrine tumors. In addition to locoregional staging, USG and CT are particularly useful for detection of liver metastases, which is crucial before any definite therapeutic planning.[1] Somatostatin receptor scintigraphy and selective intra-arterial stimulation testing with secretin have been found to have greatest sensitivity in localizing gastrinoma.[1] MRI has an important role in identification of EPNET. The use of fast spin echo (FSE) and fat saturation techniques are particularly useful in imaging pancreatic lesion especially islet cell tumor.[7]

Genetic screening in first degree relatives of MEN1 patients may be advisable during early adolescence to assess risk of developing MEN1 in future. In symptomatic individuals of MEN1, annual clinical and biochemical (calcium, PTH, gastrin, prolactin) follow-up as well as routine pancreatic and pituitary imaging may be complemented on individual merit basis.

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Painful opthalmoplegia: The Tolosa-Hunt syndrome

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A 49 year-old Filipino lady presented to us with 1 day history of generalized headache, vomiting, right eye pain and dizziness. There was no history of seizures, loss of consciousness, weakness or visual disturbances. She was hypertensive and on irregular medication. On examination she was conscious, alert and oriented. Pulse was 50/min, blood pressure 220/130, temperature 36.6°C. There was no focal neurological deficit, papillodema or evidence of meningeal irritation. Hypertension was controlled with captopril and amlodipine.

On the following day, the patient continued to have right orbital pain associated with diplopia on looking to the left. She developed features of right third nerve palsy partial ptosis, with pupil sparing. Sensory impairment in the distribution of the ophthalmic division of the fifth nerve was detected on the same side. There was no proptosis or chemosis and the fundus examination was normal. There were no long tract signs. MRI findings are shown in Figures 1, 2, and 3. Figure 4 is a follow-up MRI 6 months later after treatment with corticosteroids.

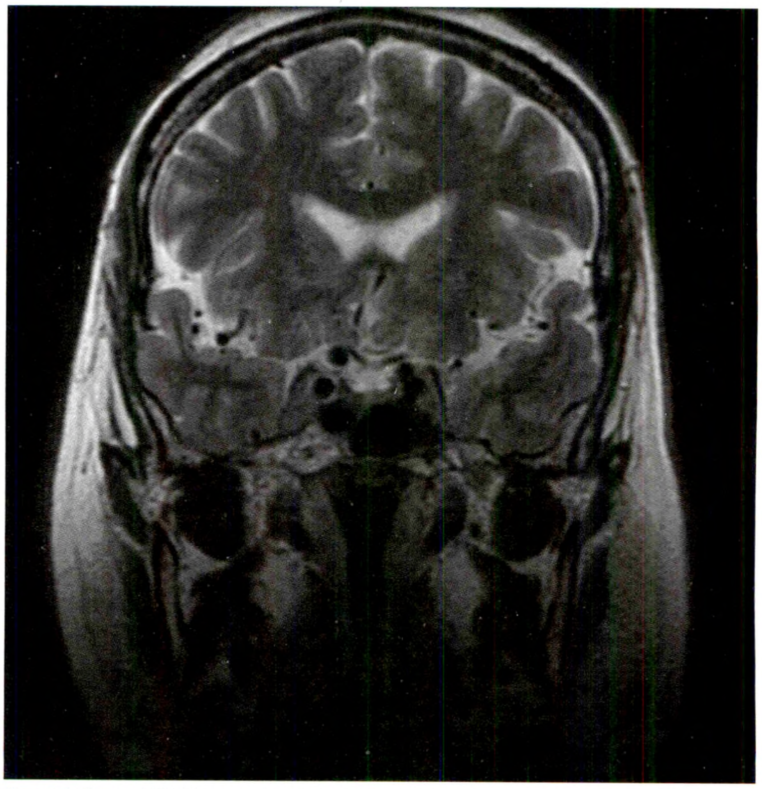

Figure 1. Coronal T2W image showing mildly hypointense abnormal soft tissue in the parasellar region.

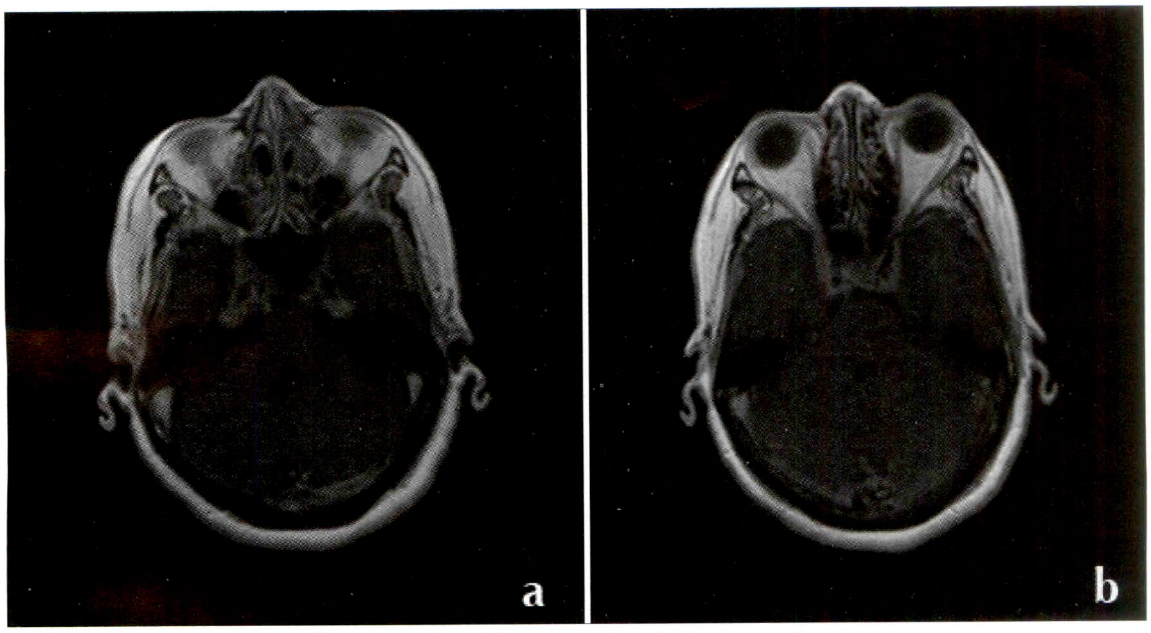

Figure 2. Axial post contrast T1W images showing enhancing soft tissue involving the parasellar region and cavernous sinuses on both sides with significantly greater involvement on the right where extension is seen to the orbital apex.

DISCUSSION

In a patient presenting with painful ophthalmoplegia, etiologies fall into three broad categories including vascular, neoplastic and inflammatory conditions. Diabetes mellitus is an important microvascular cause of painful pupil-sparing ophthalmoplegia. Tuberculosis, syphilis, mucormycosis, Herpes zoster and sinusitis are some of the infective conditions. Primary and secondary intracranial neoplasms and collagen diseases may masquerade as the Tolosa Hunt Syndrome. Intracranial aneurysms should be ruled out by MR or cerebral angiography, especially if anisocoria is detected. Essentially this syndrome remains a diagnosis of exclusion. Tolosa demonstrated granulomatous inflammation of the carotid sinus in his case at necropsy. MRI characteristically shows abnormal enhancing lesions in the cavernous sinus. Typically it is isointense with the grey matter on short TR/TE* resolution of images and iso to slightly hypointense on long TR/TE images.[1] Lateral convex bulging of the cavernous sinuses and a variable extension to the ipsilateral orbital apex, the sphenoid sinus and the floor of the middle cranial fossa and subtemporal fossa have been described. Similar signal intensity and enhancement has been described with other granulomatous lesions like sarcoidosis and tuberculosis and in lymphoma and meningiomas.[2]

The condition responds dramatically to cortico-

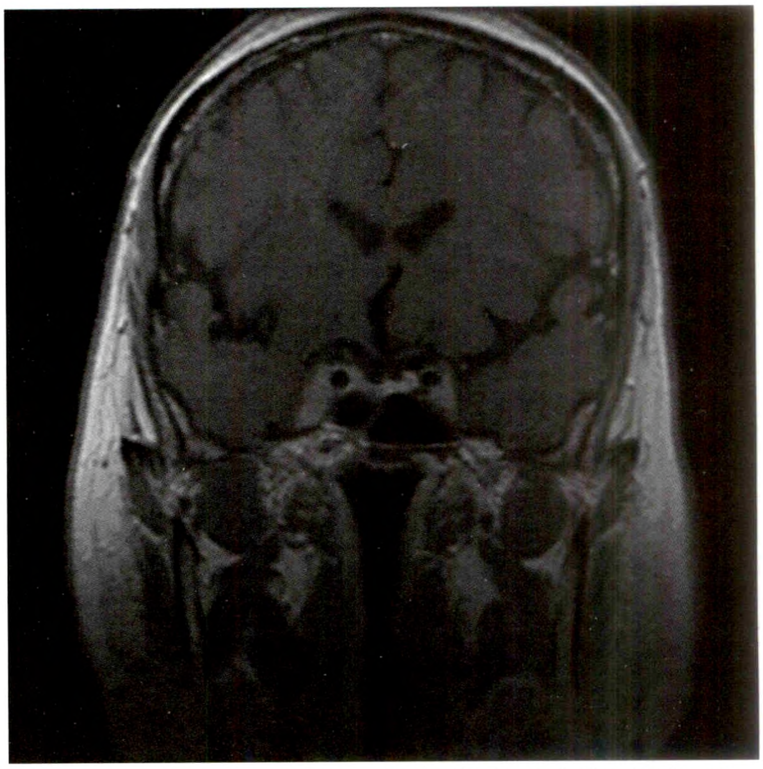

Figure 3. Coronal post contrast T1W image showing the abnormal enhancing tissue in the parasellar region causing lateral convex bulging of the cavernous sinuses.

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*Time to repetition and time to echo in spin (echo sequence of MRI).

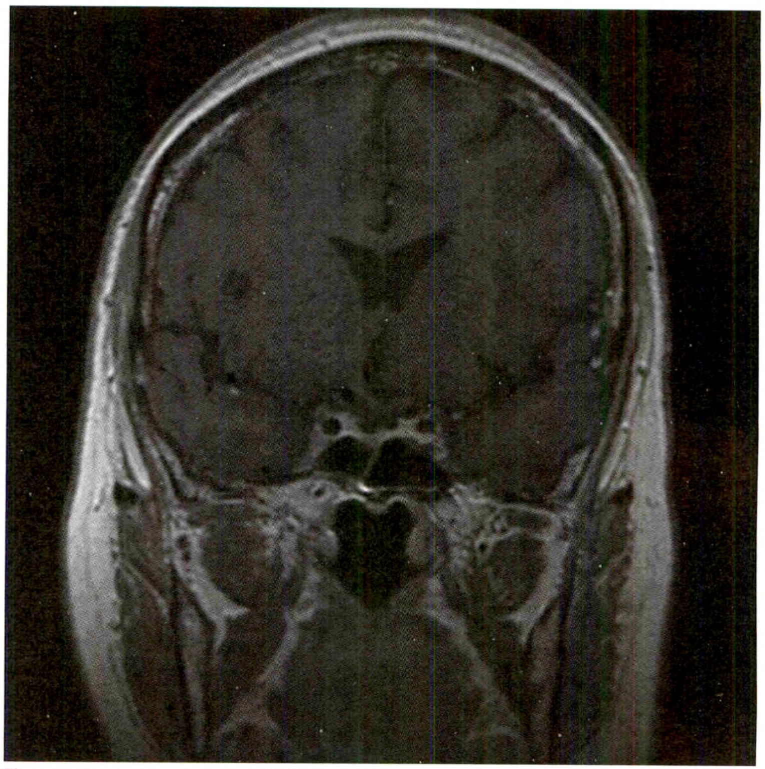

Figure 4. Post-contrast coronal T1W image showing near complete resolution of previously detected abnormality involving the parasellar region.

steroids. Pain subsides within 72 hours of initiation of corticosteroids followed by resolution of the ophthalmoplegia. Prompt response to steroids has often been used to confirm the diagnosis of Tolosa-Hunt Syndrome. However, some cases of lymphoma, sarcoidosis, Wegener's granulomatosis and intracranial aneurysms may also show partial improvement.

In 1988 Hunt and Brightman recommended that the criteria for the diagnosis of Tolosa-Hunt Syndrome should be extended to include involvement of the 2nd and 3rd division of the 5th nerve, structures which lie outside the cavernous sinus. They also downplayed the need for histological confirmation of the diagnosis. Surgical exploration and biopsy should only be considered for very early relapses or poor response to steroids.[3]

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Good reporting of trials and observational studies: Related guidelines and initiatives

CONSORT (Consolidated Standards of Reporting Trials), is part of a broader push to produce reporting guidelines (RGs) for many different types of research. The main product of CONSORT is the CONSORT Statement <http://www.consort-statement.org/index>, which is an evidence-based, minimum set of recommendations for reporting RCTs. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. The CONSORT Statement comprises a 22-item checklist and a flow diagram, along with some brief descriptive text.

ASSERT

The ASSERT <http://www.assert-statement.org/> (A Standard for the Scientific and Ethical Review of Trials) initiative is a proposed standard for the review and monitoring of randomized clinical trials by research ethics committees. Among other items, its checklist incorporates certain elements of CONSORT, to ensure fulfillment of the requirements for scientific validity in the ethical conduct of clinical research.

EQUATOR

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The MOOSE <http://www.consort-statement.org/index> (Meta-analysis of Observational Studies in Epidemiology) paper reports the outcome of a 1997 workshop to examine the reporting of meta-analyses of observational studies. It makes recommendations to aid authors, editors, reviewers and readers of observational research. (See CONSORT website)

QUOROM

The QUOROM (Quality Of Reporting Of Meta-analyses) conference resulted in the creation of the QUOROM Statement, which consists of a checklist and flow diagram. (See CONSORT website)

STARD

The STARD (Standards for Reporting of Diagnostic Accuracy) initiative aims to improve the accuracy and completeness of reporting of studies of diagnostic accuracy in order to allow readers to assess the potential for bias in a study and to evaluate the generalisability of its results. (See CONSORT website)

STROBE

STROBE <http://www.strobe-statement.org/> (STrengthening the Reporting of OBservational studies in Epidemiology) is an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and editors involved in the conduct and dissemination of observational studies.

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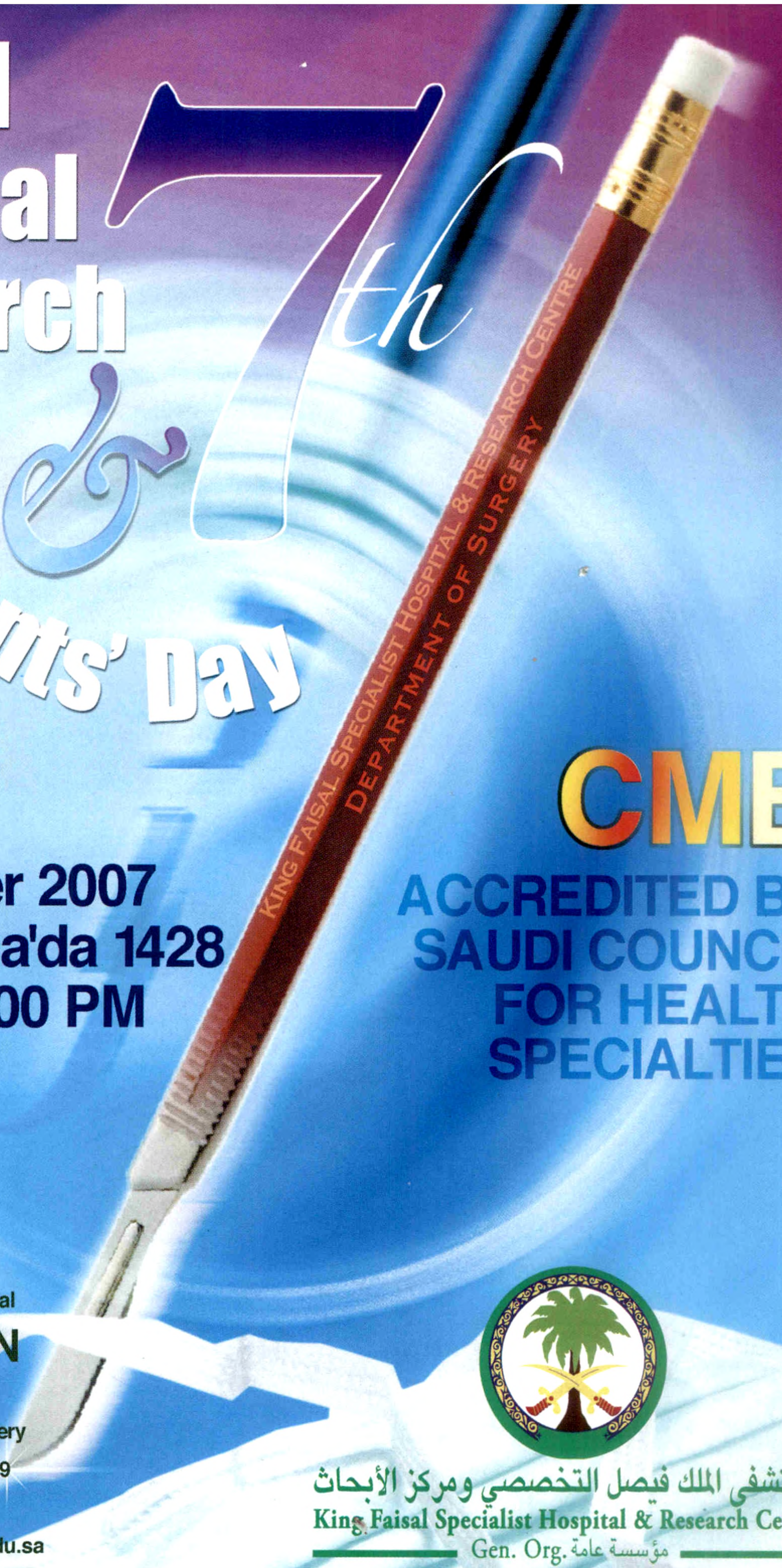

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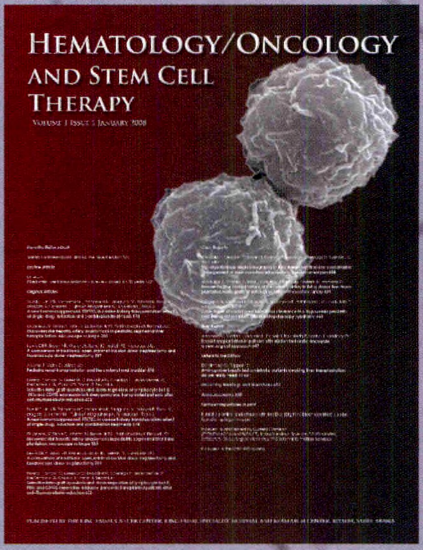

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مقارنة فحص سرعة تثفل الكريات الحمر بجهاز تحليل (Micro Test ١) والطريقة التقليدية (Westergren)

الخلفية: يبقى فحص سرعة تثفل الكريات الحمر هو الأكثر استخداماً في المختبرات لمراقبة العدوى والأمراض الالتهابية وبعض أنواع السرطانات. تم مؤخراً تطوير طرق متعددة للفحوص ونتيجة لذلك تحسنت سلامة ووثوقية فحص سرعة تثفل الكريات الحمر. الغرض من هذه الدراسة هو مقارنة طريقتين للفحص، الطريقة التقليدية اليدوية (Westergren) وطريقة جديدة شبه آلية (Micro Test ١) لتحديد سرعة التثفل.

المرضى والطرق: تم تجميع عينات الدم من ٢٠٠ مريض منوم بعد أن صاموا أثناء الليل. كانت نتائج الفحص بجهاز (Micro Test ١) لعينات الدم غير المخففة وباستخدام مضاد التخثر (K٣ EDTA) تتراوح من ٢-٨٢ مل/س وتم استخدامها للمقارنة مع طريقة (Westergren).

النتائج: أظهر التحليل التراجعي الخطي لمقارنة عمل جهاز (Micro Test ١) والطريقة التقليدية وجود معامل ترابط جيد بينهما وتراجعاً للعينات (Sy/x=١,٨٥؛ y=٤,٩١ + ٠,٨٦ x؛ P=٠,٠٠١؛ r=٠,٩١٠). لم يظهر تحليل Bland-Altman دلالة على وجود فرق واضح بين جهاز (Micro Test ١) والطريقة التقليدية.

الخلاصة: جهاز (Micro Test ١) سهل الاستعمال، وله ميزة تشغيلية جيدة، ويحتاج لصيانة بسيطة، مع قلة التماس مع المواد ذات الخطورة.

علاقة معتمدة عل العمر - ومنسب كتلة الجسم بين عوز الحديد ومقاومة الأنسولين في النساء قبل سن اليأس

المقدمة: لم تجر دراسات استباقية لتقييم تأثيرات تصحيح أنيميا عوز الحديد على مقاومة الأنسولين في النساء غير المصابات بداء السكري قبل سن اليأس. قمنا بإجراء الاستقصاءات حول هذه العلاقة على ٥٤ امرأة غير مصابة بداء السكري قبل سن اليأس مع إصابتهم بأنيميا عوز الحديد.

المرضى والطرق: تم علاج جميع المرضى بمستحضرات الحديد بالفم. وتم حساب مقاومة الأنسولين مع صيغة تقييم نموذج الاستتاب. وقمنا بتقسيم جميع المرضى حسب متوسط العمر ومنسب كتلة الجسم لتقييم العلاقة بين أنيميا عوز الحديد ومقاومة الأنسولين وكيفية تأثرهما بالعمر ومنسب كتلة الجسم.

النتائج: بالرغم من عدم حدوث تغير في مستوى الغلوكوز الصائم، إلا أنه قد تبين حدوث انخفاض ملحوظ في مستوى الأنسولين الصائم بعد تلقي علاج الأنيميا وذلك لدى النساء الأصغر سناً (‹ ٤٠ سنة) والمجموعات ذات منسب منخفض لكتلة الجسم (‹ ٢٧ كيلوغرام / متر مربع). ولكن لم يحدث ذلك لدى النساء الأكبر سناً (› ٤٠ سنة) وفي المجموعات التي لديها ارتفاع في منسب كتلة الجسم (› ٢٧ كيلوغرام/ متر مربع). وكانت مستويات الأنسولين الصائم بعد العلاج مرتبطة بشكل إيجابي مع كل من منسب كتلة الجسم ومستويات الهيموغلوبين بعد العلاج. وأظهر التحليل التراجعي بأن العوامل المؤثرة في مستويات الأنسولين بعد العلاج هي منسب كتلة الجسم ومستويات الهيموغلوبين.

الاستنتاج: أظهرت نتائجنا بأنه بعد تصحيح أنيميا عوز الحديد فإن مستويات الأنسولين وحاصل (HOMA) ينخفضان لدى النساء الأصغر سناً غير المصابات بداء السكري قبل سن اليأس.

تأثير فرط سكر الدم على وفيات السكتة الإقفارية لدى المصابين بداء السكري وغير المصابين به

المقدمة: تشير الدراسات السابقة إلى أن توسع الإحتشاء قد يكون مسئولا عن زيادة الوفيات بعد الإصابة بالسكتة لدى المرضى المصابين بفرط سكر الدم الإجهادي المطول. لذلك، قمنا بتقييم تأثير فرط سكر الدم الإجهادي المطول على وفيات السكتة لدى المصابين وغير المصابين بالسكري.

المرضى والطرق: حسبنا الترابط بين متوسط مستويات غلوكوز الدم وقت الدخول وبعد ٧٢ ساعة لدى المصابين وغير المصابين بالسكري وبين النتيجة النهائية لدى ٦٣٠ مريضا بالسكتة أدخلوا في قسم العناية المركزة خلال ٢٤ ساعة من الإصابة بالسكتة. عوملت مستويات غلوكوز الدم الأعلى من ٦,١ ملمول/ل (١٢١ ملغ/دل) باعتبارها حالة فرط سكر الدم.

النتائج: من بين ٦٣٠ مريض (متوسط العمر ٧١ ± ٦) ٤١٠ كان منهم غير مصابين بالسكري (نسبة الوفاة ٢٥ ٪) و٢٢٠ مصابين بالسكري (نسبة الوفاة٢٠٪). جميع المرضى المتوفين خلال ٢٨ يوما من التنويم أصيبوا بفرط سكر الدم (وقت الدخول وبعد ٧٢ ساعة، بالرغم من العلاج بالإنسولين). كان الإحتمال النسبي غير المعدل للوفاة داخل المستشفى خلال ٢٨ يوما لدى جميع مرضى السكتة ٠,٦٨(م ث ٩٥٪، ٠,١٤-١,٩) لغير المصابين بالسكري و ٠,٣٩ (م ث ٩٥٪، ٠,٢٧-١,٥٦) للمصابين بالسكري. وكان الإحتمال النسبي غير المعدل للوفاة داخل المستشفى خلال ٢٨ يوما لدى مرضى السكتة الإقفارية الذين بلغ متوسط مستويات غلوكوز الدم لديهم ٦,١-٨,٠ ملمول/ل (١٢١-١٤٤ ملغ/ دل) عند الدخول وبعد مرور ٧٢ ساعة ١,٨٣ (م ث ٩٥٪ ٠,٤١-٥,٥) لغير المصابين بالسكري و ١,١٣ (م ث٩٥٪، ٠,٧٨-٤,٥). للمصابين بالسكري. كان الإحتمال النسبي للوفاة داخل المستشفى خلال ٢٨ يوما لدى غير المصابين بالسكري الذين لديهم فرط سكر الدم أعلى بـ ١,٧ مرة من المرضى المصابين بالسكري.

الاستنتاج: إن فرط سكر الدم الإجهادي المطول لدى مرضى السكتة الإقفارية يزيد من احتمال الوفاة خلال ٢٨ يوما من التنويم في المستشفى خاصة لدى غير المصابين بالسكري.

الخلاصات العربية

فائدة مستوى الجلوكوز في البلازما عند الصيام في التكهن بمستوى جليكوسيل الهيموجلوبين في مرض السكر من النوع الثاني

المقدمة: مازال توفر مقايسة جليكوسيل الهيموجلوبين في الممارسة السريرة محدوداً. وقد بحثنا في العلاقة بين مستوى الجلوكوز في البلازما عند الصيام وجليكوسيل الهيموجلوبين لتحديد مستويات الجلوكوز المثلى مما يتكهن بمستوى جليكوسيل الهيموجلوبين.

المرضى والطرق: قمنا بتحليل استقصائي لبيانات ٢٨٨٨ مريضاً مصاباً بمرض السكري من النوع الثاني بعمر ≥ ٢٠ عاماً باستخدام التراجع الخطي للجليكوسيل في الهيموجلوبين مقابل مستوى الجلوكوز في البلازما عند الصيام. تم استخدام منحنىROC لتحليل الخواص لتحديد النقاط الفاصلة للجلوكوز على الصيام وعلاقته بجليكوسيل الهيموجلوبين من حيث المنطقة تحت المنحنى، والحساسية والمواصفات بالإضافة إلى ٩٥ ٪ فترات الثقة لكل نقطة فاصلة.

النتائج: كان متوسط ± (الانحراف المعياري) للفئة العمرية للمرضى ٥٢ ± ١١٫٦ عاماً. بلغ متوسط نسبة جليكوسيل الهيموجلوبين ٨٫٩ ± ٢٫٤٦ ٪. ومتوسط الجلوكوز في البلازما عند الصيام ١٠٫١± ٣٫٦٢ مليمول/ليتر. كان انتشار جليكوسيل الهيموجلوبين ≥ ٧٫٠٪ و ، ٦٫٥٪ ٧٦٪ و ٨٢٪ على التوالي. بصورة عامة، كانت هناك علاقة خطية بين مستوى الجلوكوز في البلازما عند الصيام وجليكوسيل الهيموجلوبين (r=٠٫٦٢، P=٠٫٠٠١). تكهن مستوى الجلوكوز في البلازما عند الصيام ٩٫٩، مليمول/ليتر بمستوى جليكوسيل الهيموجلوبين يصل إلى ≥ ٧٫٠٪ في منطقة دون المنحنى = ٠٫٨٠٧(٩٥٪ فترة ثقة،٠٫٠٫٧٩٤ إلى ٠٫٨٢١). بينما كان مستوى الجلوكوز في البلازما عند الصيام ، ٨٫٢ مليمول/ليتر وأنبأ بمستوى جليكوسيل الهيموجلوبين يصل إلى ≥ ٦٫٥٪ في منطقة تحت المنحنى =٠٫٨٠٥(٩٥٪ فترة ثقة،٠٫٠٫٧٩١ إلى ٠٫٨١٨). بلغت الحساسية لكلتا النقطتين الفاصلتين ٦٤٫٥٪ و ٧٠٫٧٪. أما المواصفات ٨٢٫٧٪ و ٧٦٫٤٪ أما معدل التشابه الإيجابي فهو ٣٫٧٣ وقيمة التكهن الإيجابية فهي ٩٢٫٢٪ و ٩٣٫٢٪ على التوالي.

الاستنتاج: عندما لا يتوفر تحديد جليكوسيل الهيموجلوبين، قد تستخدم مستويات الجلوكوز في البلازما عند الصيام لتحديد المرضى خارج السيطرة من المصابين بمرض السكر من النوع الثاني والبدء في تركيز العلاج بطريقة منظمة تجنباً للمضاعفات طويلة الأمد لمرض السكر.

التكهن بعدم تحمل الغلوكوز مع غلوكوز بلازما صيامي طبيعي بواسطة نموذج عناصر المتلازمة الاستقلابية

المقدمة: من المفاجئ أن يبقى ما يقدر بحوالي نصف المصابين بسكري النوع الثاني غير مكتشفين. يمكن إرجاع الأسباب المحتملة لذلك جزئيا إلى وجود أشخاص يكون غلوكوز البلازما الصيامي لديهم طبيعيا ولكن سكر الدم بعد الأكل يكون مرتفعا. حاولنا تطوير نموذج تكهني فعال باستخدام عناصر المتلازمة الاستقلابية كمعالم للتعرف على هؤلاء الأشخاص.

المرضى والطرق: خضع جميع المشاركين لاختبار تحمل الغلوكوز القياسي (٧٥ غم) بالفم والذي أظهر أن تحمل الغلوكوز طبيعي لدى ١٠٦، ومعتل لدى ٦١، وفرط سكر الدم بعد التحدي المعزول لدى ٦. اختبرنا خمسة نماذج اشتملت على عناصر مختلفة من المتلازمة الاستقلابية. النموذج صفر: غلوكوز البلازما الصيامي. النموذج ١ (نموذج التاريخ السريري): تاريخ الأسرة، غلوكوز البلازما الصيامي، العمر، الجنس. النموذج ٢ (نموذج مكونات المتلازمة السريرية): النموذج ١ زائد ثلاثيات الغليسريد، كولسترول البروتين الشحمي عالي الكثافة، منسب كتلة الجسم، ضغط الدم الانقباضي، ضغط الدم الانبساطي. النموذج ٣ : نموذج ٢ زائد إنسولين البلازما الصيامي. النموذج ٤ : نموذج ٣ زائد تقييم نموذج الاستتباب لمقاومة الأنسولين. استخدمنا منحنى ROC لتحديد التمييز التكهني لهذه النماذج.

النتائج: كانت المساحة تحت المنحنى ROC للنموذج صفر أكبر بدرجة مهمة من المساحة تحت الخط المرجعي القطري، وكانت المساحة تحت المنحنى ROCلجميع النماذج الأخرى أكبر مما هي للنموذج صفر. وبالنظر إلى بساطة النموذج ٢ وتكلفته الأقل فإنه النموذج الأفضل للاستخدام. ومع ذلك كانت المساحة تحت المنحنى للنموذج ٣ هي الأكبر.

الاستنتاج: تظهر هذه الدراسة أن النموذجين الثاني والثالث يوفران تمييزا تكهنيا أفضل بدرجة هامة للتعرف على الأشخاص ذوي الغلوكوز البلازمي الصيامي الطبيعي المعرضين بدرجة عالية لعدم تحمل الغلوكوز.

خبرة قوامها ١٢٢ عملية زرع كبد متتالية في مستشفى الملك فيصل التخصصي ومركز الأبحاث

المقدمة: المملكة العربية السعودية رائدة في الشرق الأوسط في مجال زرع الكبد من المتبرعين المتوفين ومن المتبرعين الأحياء. نستعرض في هذا المقال خبرتنا في هذا المجال في مستشفى الملك فيصل التخصصي ومركز الأبحاث خلال الفترة من إبريل ٢٠٠١م إلى يناير ٢٠٠٧م.

المرضى والطرق: أجرينا خلال هذه الفترة الزمنية ١٢٢ عملية زرع كبد (٧٧ من متبرعين متوفين و٤٥ من متبرعين أحياء) لما مجموعه ١١٨ مريضا (٤ عمليات زرع مكررة).

النتائج: كان عدد عمليات الزرع للبالغين ١٠٧ وللأطفال ١١. وكانت نسبة الذكور/الإناث الإجمالية ٥٢/٦٦. والعمر الوسطي للمرضى ٤٣ سنة (المدى ٢-٦٣ سنة). بالنسبة لمجموعة الزرع من متبرعين متوفين كان زمن العملية الوسطي ٨ ساعات (المدى ٤-١٩). ونقل الدم الوسطي ٦ وحدات (المدى ٠-٤٠). ومتوسط فترة التنويم ١٣ يوما (المدى ٦-١٨٣). وكانت نسبة البقيا الإجمالية للمرضى والطعوم ٨٦٪ بعد فترة متابعة متوسطها ٧٦٠ يوما (المدى ٢-٢٠٨٥). أما بالنسبة لمجموعة الزرع من متبرعين أحياء فقد كان زمن العملية الوسطي ١١ ساعة (المدى ٧-١٧). ونقل الدم الوسطي ٤ وحدات (المدى ٠-٦٥). ومتوسط فترة التنويم ١٥ يوما (المدى ٧-١٢٧). وكانت نسبة البقيا الإجمالية للمرضى والطعوم ٩٠٪ و٨٠٪ على التوالي بعد فترة متابعة متوسطها ٦٨٥ يوما (المدى ٢٦-١٥٤٠) مع عدم وجود فرق مهم في نسبة البقيا للمرضى والطعوم بين المجموعتين. كان كل من المضاعفات الصفراوية والوعائية في مجموعة الزرع من أحياء أعلى بدرجة مهمة مما هي في مجموعة الزرع من متوفين (P<٠,٠٥).

الاستنتاج: تجرى عمليات الزرع من متبرعين متوفين وأحياء بنجاح في مستشفى الملك فيصل التخصصي ومركز الأبحاث. ولكن النتائج الأولية تشير إلى نسبة أعلى من المضاعفات الصفراوية والوعائية في مجموعة المتبرعين الأحياء.

المدونـــات الطبيـــة السعوديـــة

السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصّصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول مكتب المطبوعات (ر.إ ٣٦).

سعر الاشتراك ١٠٠ ريال في السنة للأفراد داخل المملكة و٢٠٠ ريال في السنة للأفراد خارج المملكة و٥٠٠ ريال في السنة للمؤسسات. يمكن فتح اشتراك مجاني للأفراد و المؤسسات في الدول النامية.

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تصدر المدونات الطبية السعودية مرة كل شهرين عن مستشفى الملك فيصل التخصصي ومركز الأبحاث . ص.ب ٣٣٥٤ . الرياض ١١٢١١. المملكة العربية

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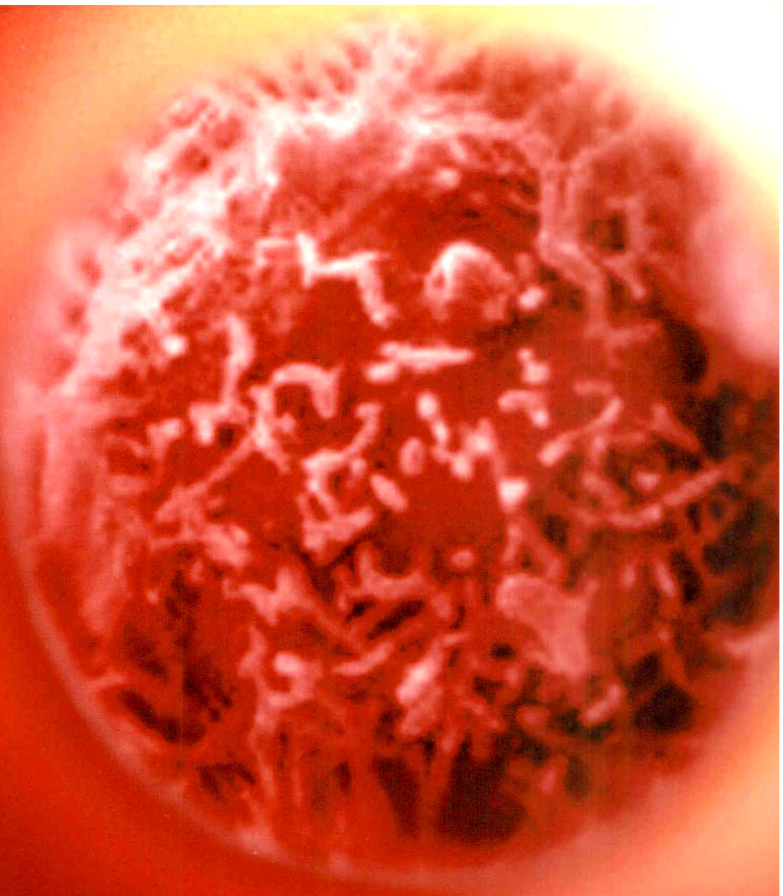

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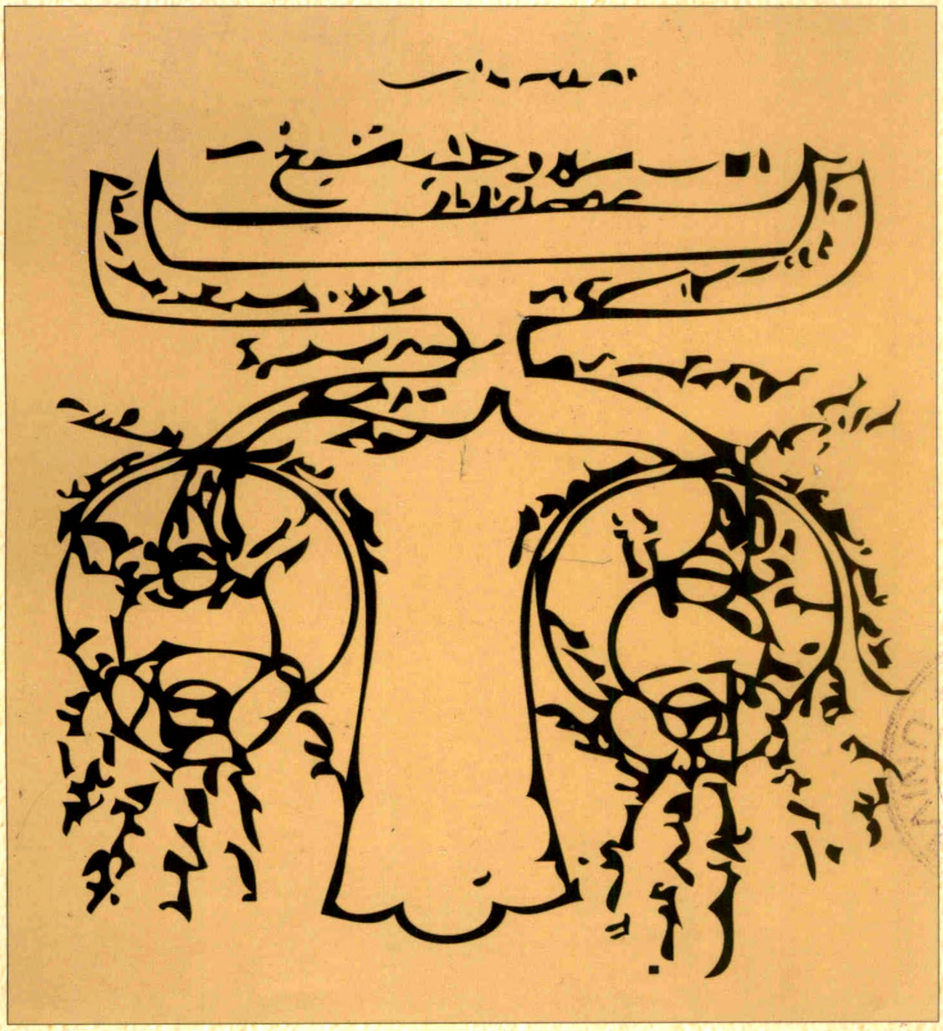

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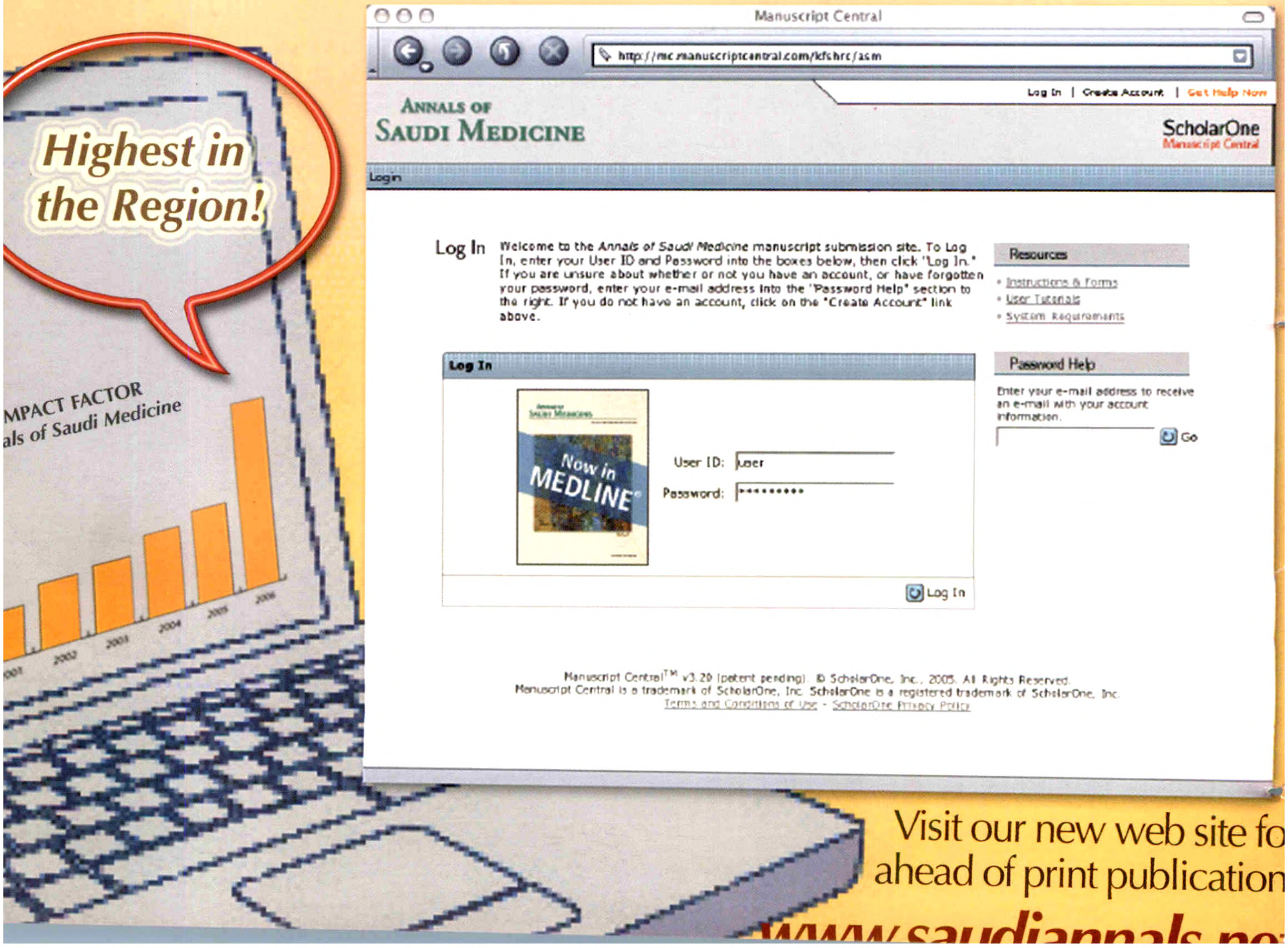

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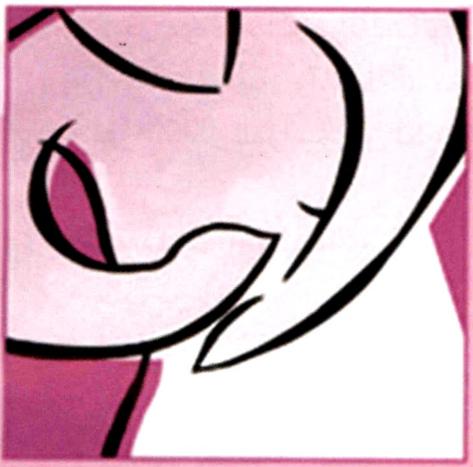

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إعــلان

يسر إدارة الإبتعاث والتدريب بالتعاون مع إدارة التمريض بمستشفى الملك فيصل التخصصي ومركز الأبحاث (مؤسسة عامة) أن تعلن عن رغبتها في إتاحة الفرصة للدراسة والتدريب في جامعة الملك سعود بن عبدا لعزيز للعلوم الصحية (كلية التمريض والعلوم الطبية المساعدة) للفتيات السعوديات والحصول على درجة البكالوريوس في علوم التمريض للفصل الدراسي القادم (**سبتمبر ٢٠٠٦**)

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- سعودية الجنسية
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- إجتياز الاختبار والمقابلة الشخصية المعد من قبل (**كلية التمريض والعلوم الطبية المساعدة**)
- تفرغ كامل للدراسة وان تكون لائقة جسدياً

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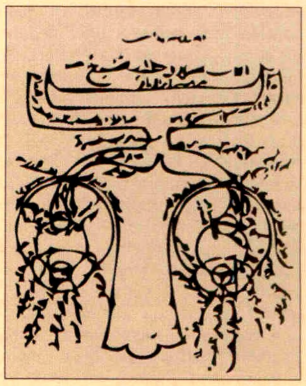

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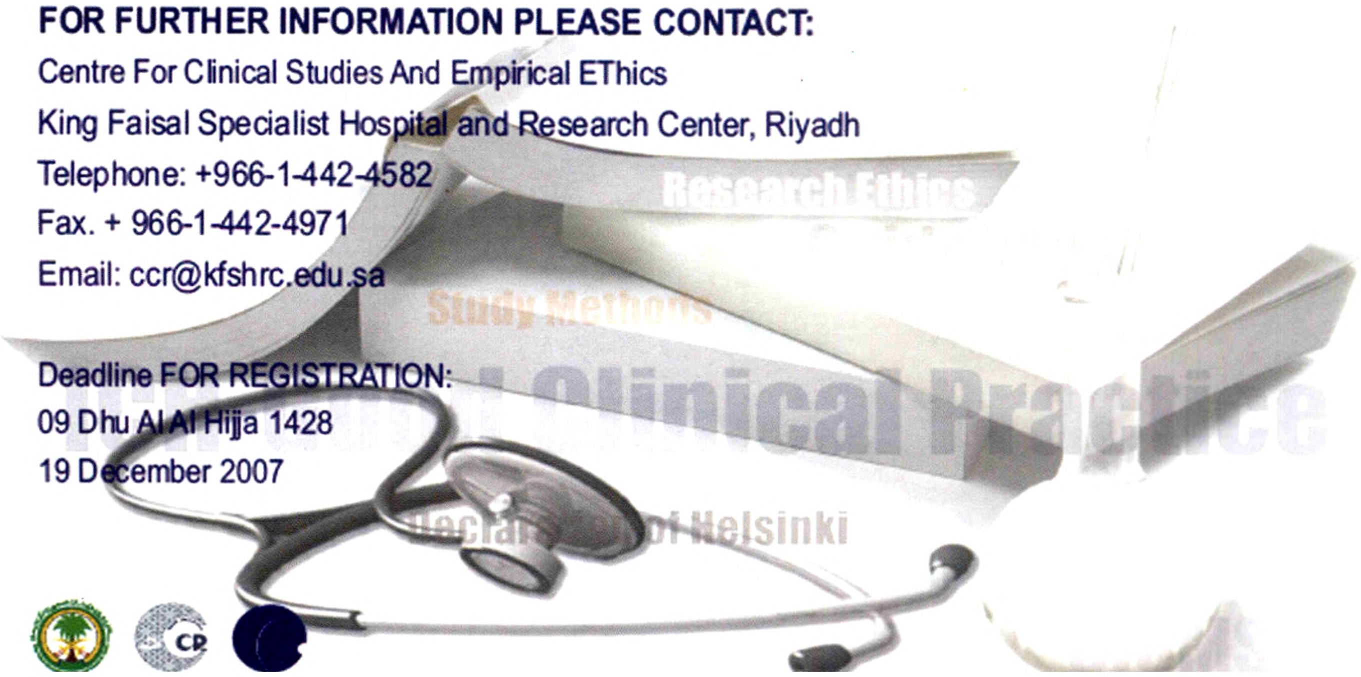

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summary of original articles

FAMILY MEDICINE

The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials

Alkhenizan and Hafez identified 12 randomized controlled trials with 167 025 participants that addressed the role of vitamin E in cancer prevention and that were of sufficient quality to include in a meta-analysis. Primary outcomes were total mortality, cancer mortality, total incidence of cancer and incidence of individual cancers. Compared to control groups, there were no statistically significant differences in any primary outcome for any cancer except prostate cancer. They concluded that vitamin E supplementation could be used in groups of men at high risk of prostate cancer (>55 years of age, elevated prostate specific antigen, African Americans, and patients with a family history of cancer).

CARDIOLOGY

Comparison of gated SPECT, echocardiography and cardiac magnetic resonance imaging for the assessment of left ventricular ejection fraction and volumes

Demir and colleagues examined the concordance betweeen LVEF, EDV and ESV obtained by SCHO, GSPECT and CMRI in 21 patients with suspected coronary artery disease. They found good overall correlations, concluding that LVEF obtained from any of the three imaging modalities could be used interchangeably, but that care should be taken in comparing LV volumes.

PULMONOLOGY

Predictors of obstructive sleep apnea in snorers

Ibrahim and colleagues examined the contribution of possible risk factors for OSA in snorers referred for polysomnography by means of a questionnaire. OSA was indicated by a respiratory disturbance index of >5 events/hour. In a multivariate analysis that included data on 126 subjects, male gender, the Epworth Sleepiness Scale, and a history of witnessed apneas were the most important predictors of OSA. Increased body mass index was linked to OSA only in females.

RHEUMATOLOGY

Bone mineral density in children with systemic lupus erythematosus and juvenile rheumatoid arthritis

In a cross-sectional study, Kashef and colleagues compared BMD in 20 children with SLE or JRA and 20 healthy control children. BMD in the patients was significantly lower than in the controls ($P<0.001$), with the severity of decreased BMD more prominent in the lumbar vertebrae. None of several disease-related variables (cumulative dose of steroids, daily dose of steroid, disease duration, disease activity, height, weight and age) were consistently related to decreased BMD.

INFECTIOUS DISEASE

The prevalence and degree of *Plasmodium falciparum* to first-line antimalarial drugs: an in vitro study from a malaria endemic region in Yemen

In 219 *P. falciparum* malaria patients, Al-Shamahy and colleagues found chloroquine resistance in 47% of isolated *P. falciparum* schizonts, mefloquine resistance in 5.2% and no resistance against quinine or artemisinin. The study confirmed the slow rate in the rise of resistance against chloroquine in Yemen, which is likely to continue. The rate of mefloquine resistance is lower than in Africa or Southeast Asia, but this is the first report of mefloquine resistance in Yemen.

PATHOLOGY

Clinicopathologic features of hepatic neoplasms in explanted livers: a single institution experience

Mourad and colleagues found 15 neoplasms in 98 liver transplants (15.3%). The primary etiology of hepatic disease was hepatitis C virus. The primary tumor was hepatocellular carcinoma. The authors note that tumors can be incidentally identified in explanted livers, are frequently not associated with elevated levels of serum alpha-fetoprotein and CA19-9, are multifocal but small, and are associated with good prognosis. Serum alpha-fetoprotein, albeit specific, is not a very sensitive marker in the detection of hepatic neoplasms.

The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials

Abdullah Alkhenizan, Kevin Hafez

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BACKGROUND: There are conflicting results in published randomized controlled trials (RCTs) on the role of vitamin E in the prevention of cancer. We conducted a meta-analysis of RCTs to evaluate the role of vitamin E in the prevention of cancer in adults.

METHODS: We included RCTs in which the outcomes of the intake of vitamin E supplement alone or with other supplements were compared to a control group. The primary outcomes were total mortality, cancer mortality, total incidence of cancer, and incidence of lung, stomach, esophageal, pancreatic, prostate, breast and thyroid cancers. All identified trials were reviewed independently by the two reviewers to determine whether trials should be included or excluded. The quality of all included studies was scored independently by the two reviewers.

RESULTS: Twelve studies, which included 167 025 participants, met the inclusion criteria. There were no statistically significant differences in total mortality (relative risk, 0.99; 95% CI 0.96-1.03), cancer incidence (odds ratio, 0.96; 95% CI 0.92-1.01), and cancer mortality (odds ratio, 1.00; 95% CI, 0.96-1.03) among the different groups of patients included in this meta-analysis. Vitamin E was associated with a significant reduction in the incidence of prostate cancer (relative risk, 0.85; 95% CI, 0.73-0.96, number needed to treat=500), but it did not reduce the incidence of any other types of cancer.

CONCLUSIONS: Vitamin E supplementation was not associated with a reduction in total mortality, cancer incidence, or cancer mortality, but it was associated with a statistically significant reduction in the incidence of prostate cancer. Vitamin E can be used in the prevention of prostate cancer in men who are at high risk of prostate cancer.

Three types of cancer account for at least 50% of new cases in each sex: prostate, lung, and colorectal cancers in males, and breast, lung, and colorectal cancers in females. Almost one-third of cancer deaths in men and almost one-quarter in women are due to lung cancer alone. Cancer is the leading cause of potential years of life lost (PYLL) for men and women in Canada.[1] Simple, accessible and safe preventive therapies that will decrease the incidence and mortality of cancer are expected to have a great effect on public health.

Several in vitro studies showed antioxidant vitamins to have a significant protective effect against cancer.[2-4] In experimental animals deficiencies of vitamin E were associated with enhanced carcinogenesis, while supplementation of vitamin E inhibited tumor formation.[5,6]

Alpha-tocopherol is the most common naturally occurring compound of vitamin E. The recommended dietary allowance of vitamin E is 15 mg daily for adult men and women. Each 1 mg of vitamin E equals to 1.5 IU of natural vitamin E and 2.2 IU of synthetic vitamin E. Vegetable oils, nuts, and green leafy vegetables are the main dietary sources of vitamin E.[7]

METHODS

Inclusion criteria

Data sources were randomized controlled trials (RCTs) in which outcomes related to cancer prevention that were associated with the intake of vitamin E supplements alone or with other supplements were compared to a control group (placebo or control). Participants in

Table 1. Characteristics of 12 trials included in the meta-analysis.

Study	Duration	Participants	Interventions	Jadad Score
Women's Health Study, 2005[10]	10.1 years	39 876 healthy US women	Vitamin E or placebo and aspirin or placebo, using 2×2 factorial design	5
Blot et al, 1993[11]	5.25 years	29 594 healthy adults	Four combinations of vitamins including vitamin E, using 2×4 fractional design	5
ATBC, 1994;[12] Heinonen et al, 1998;[15] Albanes et al, 2000;[13] Virtamo et al, 2000[14]	6.1 years	29 133 male smokers	Vitamin E (50 mg/d), or beta-carotene (20 mg/day), both or placebo	5
MRC/BHF Heart Protection Study, 2002[16]	5 years	20 536 UK adults with coronary artery disease, other occlusive arterial disease, or diabetes	Vitamin E 600 mg/d, vitamin C 250 mg, and B-carotene 20 mg daily, or matching placebo	5
Herberg et al, 2004[17]	7.5 years	13 017 French adult men and women	Vitamin E 30 mg, B-carotene 6000 µg, vitamin C 120 mg, selenium 100 µg, zinc 20 mg or placebo	5
GISSI-Prevenzione, 1999[18]	3.5 years	11 324 Patients with recent (<3 months) MI	Vitamin E (300 mg daily, n=2830), n-3 PUFA (1g daily, n=2,836), both (n=2,830), or none (control n=2,828)	3
HOPE, 2000[19]	4.5 years	9541 patients at high risk for cardiovascular disease.	Vitamin E 400 IU or matching placebo	5
PPP, 2001[20]	3.6 years	4495 patients with one or more risk factors for cardiovascular disease	Vitamin E (300 mg/d), and no vitamin E groups, and aspirin (100 mg/day) and no aspirin groups	3
AREDS, 2001[21]	6.3 years	4754 healthy adults	Vitamin E 400IU, vitamin C 500mg, and beta carotene, and placebo	5
Li et al, 1993[22]	6 years	3318 patients with cytological evidence of esophageal dysplasia	Daily supplementation with 14 vitamins including vitamin E (60 IU/d) and 12 minerals, or matching placebo	5
Davey et al, 1998[23]	510 days	2002 patients with angiographically proven coronary atherosclerosis	Vitamin E (800 IU/d for first 546 patients, 400 IU/d for reminder), or matching placebo	5
Boaz et al, 2000[24]	519 days	196 hemodialysis patients with pre-existing cardiovascular disease	Vitamin E 800 IU/d, or matching placebo	5

studies were adults of either sex (18 years or older). Types of interventions were vitamin E alone or with other supplements versus placebo or no intervention. Supplementation was in capsule or tablet form, to be consumed by mouth.

At least one of the following primary outcomes must have been reported: total mortality, cancer mortality, total incidence of cancer, or incidence of lung, stomach, esophageal, prostate, breast, urinary, hematological or thyroid cancers. Secondary outcomes were the role of high dose (≥300 mg/d) and low dose (<300 mg/d) vitamin E on the primary outcomes.

Search strategy for identification of studies

The following bibliographic databases were searched to identify the relevant primary studies: The Cochrane Controlled Trials Register (CCTR), MEDLINE, and EMBASE. A computerized search of MEDLINE was performed using the OVID platform, to search the MEDLINE database for articles published between January 1966 and June 2005, and the EMBASE database from 1980 to June 2005. The search strategy was conducted using the MeSH terms: "antioxidants" "vitamins", "vitamin E", "alpha-tocopherol", "tocopherol", "cancer", "prevention", and "randomized controlled trials". These terms were used in various combinations. The Cochrane library was searched for relevant articles using the same search strategy. Relevant articles were retrieved through a manual review of references. No language restrictions were applied.

Study selection

All identified trials were reviewed independently by the two reviewers to assess methodological quality and determine whether trials should be included or excluded. Disagreement was resolved by discussion. All selected studies were published studies. The same two reviewers assessed the methodological quality of each trial according to Jadad score.[8] After independent evaluation, the two reviewers discussed the results for each study and any discrepancy was resolved by discussion.

Data abstraction and synthesis

Data were independently extracted by the same reviewers and cross-checked with discrepancies resolved by discussion. The Cochrane Statistics package RevMan, version 4.2 was used for data synthesis. Relative risk (RR) and risk difference (RD) with 95% confidence intervals were reported. If there was a statistically significant RD, the number needed to treat (NNT) and number needed to harm (NNH) were calculated.

Heterogeneity was tested using the Cochran Q statistic with significance at $P<0.10$. In addition, we tested heterogeneity using the I2 method with a value greater than 50% considered to indicate substantial heterogeneity.[9] Potential sources of heterogeneity of treatment effect were explored using pre-specified subgroup analysis when there were sufficient studies to analyze the dose of vitamin E, the use of other vitamins with vitamin E, and study quality variability. Whenever there was statistically significant between-study heterogeneity the weighted estimate of the typical treatment effect across trials (relative risk) was calculated using the random effects model to ensure robustness of the results.

Description of studies and methodological quality

Twelve trials, which included 167 025 individuals, met the inclusion criteria (Table 1). More than 76 000 (45%) of the participants were females. These trials were performed in many countries (Finland, Italy, Canada, China, UK, US, Denmark, Germany, Ireland, Netherlands, Norway, Spain, Sweden, Switzerland, and Mexico). Vitamin E dose varied between 50 mg/d to 800 mg/d. Study duration ranged between 510 days to 10 years. Two studies were open-label trials, but outcome assessment was blinded in these studies.[18,20] All studies were analyzed using the intention to treat

Table 2. Summary of results of meta-analysis.

Outcomes	No. of studies	No. of participants	Relative risk (fixed) (95% CI)
Vitamin E (all studies) vs. control			
Total mortality	12	161 349	0.99 (0.96, 1.03)
Cancer mortality	6	124 495	1.02 (0.95, 1.09)
Cancer incidence	8	151 372	0.98 (0.94, 1.02)
Stomach cancer	6	134 996	1.01 (0.90, 1.15)
Lung cancer	5	111 635	1.02 (0.88, 1.19)
Colorectal cancer	4	91 099	0.95 (0.81, 1.12)
Prostate cancer	4	71 759	0.85 (0.74, 0.96)
Breast cancer	3	62 158	0.99 (0.90, 1.10)
Esophageal cancer	3	45 643	1.00 (0.88, 1.14)
Hematological cancer	2	33 277	0.98 (0.71, 1.33)
Urinary tract cancer	2	27 314	1.25 (0.84, 1.84)
Vitamin E alone vs. control			
Total mortality	6	36 465	1.00 (0.94, 1.05)
Colorectal cancer	2	24 114	1.05 (0.79, 1.39)
Prostate cancer	2	24 114	0.86 (0.70, 1.06)
Total cancer	3	19 694	1.00 (0.90, 1.12)
Cancer mortality	3	15 395	1.02 (0.83, 1.26)
Vitamin E with other supplements vs. control			
Total mortality	6	99 877	0.99 (0.96, 1.03)
Total cancer	6	106 454	0.96 (0.92, 1.01)
Cancer mortality	5	93 417	1.00 (0.93, 1.08)
Prostate cancer	3	62 218	0.79 (0.67, 0.93)
Vitamin E ≥ 300 mg/d			
Total mortality	7	52 861	1.01 (0.97, 1.06)
Cancer mortality	4	41 607	1.04 (0.92, 1.17)
Cancer incidence	4	45 906	0.98 (0.92, 1.05)
Lung cancer	2	30 077	0.97 (0.81, 1.16)
Prostate cancer	2	30 077	0.94 (0.79, 1.11)
Vitamin E < 300 mg/d			
Total mortality	4	74 584	0.97 (0.92, 1.02)
Cancer mortality	3	61 547	0.98 (0.90, 1.06)
Cancer incidence	4	74 584	0.96 (0.91, 1.01)
Stomach cancer	4	74 584	0.96 (0.84, 1.10)
Lung cancer	2	41 682	0.97 (0.85, 1.10)
Prostate cancer	2	41 682	0.69 (0.55, 0.87)

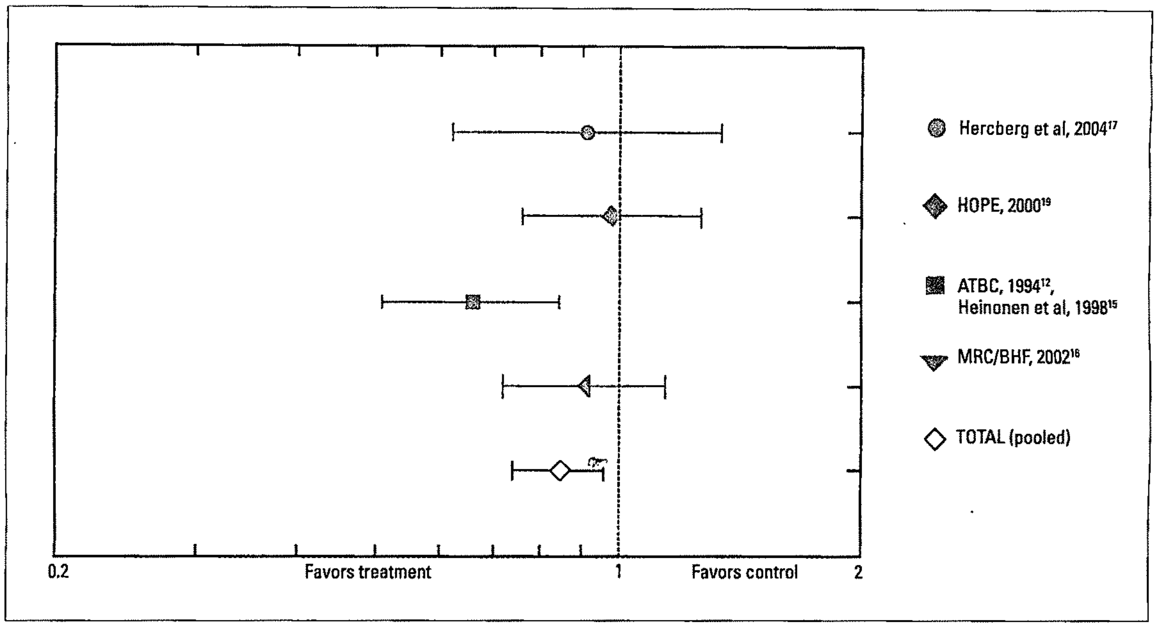

Figure 1. Relative risk (fixed) and 95% confidence intervals for prostate cancer vs. controls associated with vitamin E alone or with other supplements. Test for heterogeneity: χ^2=5.70; df=3 (*P*=0.13), F=47.4%. Test for overall effect: Z=2.50 (*P*=0.01).

Table 3. Data from four randomized, controlled trials that evaluated the role of vitamin E in the prevention of prostate cancer, and used in the pooled analysis (Figure 1).

Symbols from Figure 1	Study	Treatment group (n/N)	Control (n/N)	Weight (%)
◎	Hercberg et al, 2004[17]	49/6364	54/6377	11.34
◇	HOPE, 2000[19]	116/4761	119/4780	24.96
▣	ATBC, 1994[12]; Heinonen et al, 1998[15]	99/14 472	151/14 469	31.74
▽	MRC/BHF, 2002[16]	138/10 269	152/10 267	31.95
◇	Total (pooled analysis)	402/35 866	476/35 893	100.00

Test for heterogeneity: χ^2=5.70; df=3 (*P*=0.13), F=47.4% Test for overall effect: Z=2.50 (*P*=0.01).

principle.

RESULTS

For vitamin E alone or with other supplements versus control (all 12 studies), vitamin E was associated with a significant reduction in the incidence of prostate cancer, but did not reduce the incidence of any other types of cancer (Table 2). Four studies (including 71 759 individuals) reported on the role of vitamin E in the prevention of prostate cancer (Figure 1, Table 3).[15-19] One study showed a statistically significant reduction in the incidence of prostate cancer in individuals receiving vitamin E supplements (RR 0.66; 95% CI 0.51, 0.84).[15] When all studies were combined there was a significant reduction in the incidence of prostate cancer (RR 0.85; 95% CI 0.74, 0.96, RD=-0.002, NNT=500, test for heterogeneity: P=0.13, I2=47%)

In studies with vitamin E alone versus control (6 studies) there was no statistically significant reduction in any of the outcomes (Table 2). Two studies (including 24 114 individuals) evaluated the role of vitamin E alone in the prevention of prostate cancer (RR 0.86; 95% CI 0.70, 1.06).[15-19]

In studies of vitamin E and other supplements vs. control, vitamin E was associated with a significant reduction in the incidence of prostate cancer, but did not reduce the incidence of any other types of cancer (Table 2). Three studies (including 62 218 individuals) evaluated the role of vitamin E with other supplements in the prevention of prostate cancer (RR 0.79; 95% CI

Table 4. Ongoing studies to evaluate the effect of Vitamin E and other interventions on disease prevention.

Study	Participants	Interventions	Outcomes
Physicians Health Study II (PHS II) (Christen et al 2000[29])	15 000 US male physicians aged 55 years and older with no history of cancer, or cardiovascular disease	Vitamin E or beta-carotene or Vitamin C or a daily multivitamins or placebo in a factorial design.	Total and prostate cancer, CVD, and eye disease
Women's Atherosclerosis Cardiovascular Study (WACS) (Manson et al 1995[30])	8000 female nurses with history of cardiovascular disease	Vitamin E 400IU/d or vitamin C 1g/d, or B-carotene 20 mg/d, in a factorial design	Cardiovascular disease morbidity and mortality, cancer incidence as a secondary outcome
SELECT Trial (Lieberman 2001[26]; Lippman 2005[25])	32 400 Healthy men at least 50 years of age	Placebo or selenium (200 mcg and/or vitamin E 400 IU/day)	Prostate cancer incidence and mortality

0.67, 0.93, NNT=450, test for heterogeneity: P=0.16, I2=46%).[15-17]

With a high dose of vitamin E (≥300 mg/d) there was no statistically significant reduction in any of the outcomes in studies that used a high dose of vitamin E (Table 2). Two studies (including 30 077 individuals) evaluated the role of a high dose of vitamin E in the prevention of prostate cancer (RR 0.94; 95% CI 0.79, 1.11).[16,19]

With a low dose of vitamin E (<300 mg/d), vitamin E was associated with a significant reduction in the incidence of prostate cancer, but did not reduce the incidence of any other types of cancer that was available for analysis (Table 2). Two studies (including 41 682 individuals) evaluated the role of low dose of vitamin E in the prevention of prostate cancer (RR 0.69; 95% CI 0.55, 0.87, NNT=380, test for heterogeneity: P=0.31, I2=1.6%).[15,17]

DISCUSSION

The methodological quality of the included trials was high. Vitamin E had no effect on total mortality, cancer incidence and cancer mortality among the different groups of patients included in this meta-analysis. The only positive effect of vitamin E was in the reduction of the incidence of prostate cancer. This effect disappeared when we analyzed studies that evaluated the role of vitamin E alone; however, the sample size was insufficient (21 634 male patients) to have enough power to detect a difference in the incidence of prostate cancer. A minimum of 32 000 participants is needed to detect a difference in the effect of vitamin E on the incidence of prostate cancer.[25,26]

The effect of vitamin E in the reduction of prostate cancer was statistically significant in studies that evaluated the role of vitamin E combined with other supplements. In this analysis we had a large sample size of 62 000 participants, which allowed enough power to detect a difference in the incidence of prostate cancer.

There was no statistically significant reduction of prostate cancer in studies that used high dose of vitamin E (>300 mg); however, in this analysis the sample size was insufficient (22 515 male patients) to have enough power to detect a difference in the incidence of prostate cancer. There was a statistically significant reduction of prostate cancer in studies that used a low dose of vitamin E (<300 mg) and there was enough power to detect a difference in the incidence of prostate cancer.

Vitamin E supplementation results in a minimum of 0.2% absolute reduction in the incidence of prostate cancer, which can be translated into a a number needed to treat (NNT) of 500. This effect of vitamin E is important as prostate cancer is the leading form of cancer diagnosed in men, affecting 0.7% of the male population1. Vitamin E was well tolerated in all of the included trials. Previous meta-analysis showed that vitamin E did not affect the rate of coronary and cerebrovascular events.[27,28]

In conclusion, vitamin E supplementation can be used for the prevention of prostate cancer among high risk groups, including individuals >55 years old, patients with elevated prostate specific antigen (PSA), African Americans, and patients with family history of prostate cancer. The results of the SELECT trial and other ongoing trials (Table 4) will provide more precise answers on the role of vitamin E in the prevention of prostate cancer.

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original article

Comparison of gated SPECT, echocardiography and cardiac magnetic resonance imaging for the assessment of left ventricular ejection fraction and volumes

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BACKGROUND: Left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and end-systolic volume (ESV) can be determined non-invasively by two-dimensional echocardiography (ECHO), gated single photon emission computed tomography (GSPECT) and cardiac magnetic resonance imaging (CMRI). This study was designed to analyze the concordance between LVEF, EDV and ESV values derived from ECHO, GSPECT and CMRI.

METHODS: ECHO, GSPECT and CMRI were performed in a group of 21 patients with suspected coronary artery disease. LVEF, EDV and ESV values were calculated.

RESULTS: The mean LVEF measured with GSPECT, ECHO and CMRI were 55.9±17.8%, 55.7±16.4% and 56.4±15.7%, respectively. The mean EDV measured with GSPECT, ECHO and CMRI were 109.2±42.4 mL, 127.5±42.2 mL and 91.1±38.0 mL, respectively. The mean ESV measured with GSPECT, ECHO and CMRI were 54.2±41.2 mL, 59.9±37.6 mL and 41.8±26.9 mL, respectively. The results of linear regression analysis showed very good correlation between LVEF and ESV values derived from GSPECT, ECHO and CMRI ($r=0.91$, $r=0.92$, $r=0.97$ for LVEF and $r=0.86$, $r=0.91$, $r=0.91$ for ESV, $P<0.01$). Good correlations were found between EDV values obtained from GSPECT, ECHO and CMRI ($r=0.71$, $r=0.68$, $r=0.73$, $P<0.01$). Agreement between these techniques in LVEF values was also good, but not in LV volumes, according to Bland-Altman plots.

CONCLUSIONS: This study showed good overall correlations between LVEF, EDV and ESV values derived from GSPECT, ECHO and CMRI. LVEF obtained from any of these three imaging modalities could be used interchangeably. However, care should be taken in comparing LV volumes.

Left ventricular function and volumes have major diagnostic and prognostic importance in patients with various cardiac diseases. [1] Nowadays several noninvasive techniques are available for this purpose, including 2- or 3-dimensional echocardiography (ECHO), cardiac magnetic resonance imaging (CMRI), radionuclide ventriculography (RNV) and myocardial gated SPECT (GSPECT).[1-3] Since all of these techniques have some advantages or limitations none of them is considered a gold standard. Recently, GSPECT has been proposed for the determination of left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and end-systolic volume (ESV). GSPECT offers the potential advantage of combining information on myocardial function and perfusion without any extra cost, discomfort and radiation risk to patient.[4-7]

According to previously published studies, GSPECT correlates well with both ECHO and CMRI with respect to LVEF, LV volumes and wall motion.[1,4-19] The aim of this prospective study was to analyze the concordance between LVEF, EDV and ESV values derived from GSPECT, ECHO, and CMRI in the same group of patients.

METHODS

Twenty-one patients with known or suspected coronary artery disease, referred for routine GSPECT imaging, were included in the study. All patients underwent ECHO and CMRI. All investigations were completed within 4 weeks. There were no cardiac events between the three studies. Cardiac medications were not changed during the study. Patients who had a history of severe valvular disease, morbid obesity, pregnancy or who had myocardial infarction, angioplasty or bypass surgery during the 6 weeks before participation in the study were excluded.

GSPECT acquisition was started after 45 minutes of the intravenous injection of 555 MBq of 99mTc-methoxyisobutyl-isonitrile (99mTc-MIBI) at resting condition. Data acquisition was performed with a single-head SPECT system (ADAC Laboratories, Milpitas, California, USA) equipped with a low-energy, high-resolution collimator. A 20% window around the 140 keV energy peak of 99mTc-MIBI was used. The acquisition matrix size was 64×64×16. A total of 64 projections (step-and-shoot mode, 30 s per projection) were obtained over a 180° circular orbit. Acquisitions were gated for eight frames per cardiac cycle. The images were reconstructed using filtered back-projection. The resulting transaxial slices were re-oriented perpendicular to the heart's long axis, yielding long- and short-axis tomograms. The LVEF and left ventricular volumes were calculated using previously validated and commercially available automated software (Auto SPECT, Autoquant, ADAC Laboratories, Milpitas, California, USA; developed at Cedars-Sinai Medical Center, Los Angeles, California, USA) from the GSPECT images.

ECHO was performed with a Toshiba SSA-390-A ultrasound machine (Toshiba Medical Systems, Nasu, Japan) by one experienced cardiologist blind to the results of the GSPECT study. All images were obtained with a second harmonic mode. Two-dimensionally guided M-mode recordings were taken from the parasternal long-axis view according to the criteria of the American Society of Echocardiography. EDV, ESV and LVEF were derived from apical four-chamber and two-chamber views with the previously validated modified Simpson's biplane discs method.[20,21]

All CMRI studies were performed on a 1.5-T MR scanner (Philips Gyroscan Intera Master, Einthoven, Netherlands) with a 30 mT/m maximum gradient strength and a 150 mT/m per millisecond slew rate using a synergy body coil. Our routine CMRI protocol started with the reference images of Balanced Turbo Field Echo (B-TFE) in sagittal, axial and coronal planes, and was followed by coil sensitivity (SENSE) reference images. ECG gated, breath hold of T2 weighted B-FFE sequence (TR/TE=3.1/1.5, matrix: 256×256) in four chambers, left ventricle short axis and long axis planes were performed.

Values of LVEF, EDV and ESV derived from all three investigations were compared. Continuous data were expressed as the mean±SD. The agreement between LVEF, EDV and ESV derived from GSPECT, ECHO and CMRI data was determined with linear regression (Pearson's correlation coefficient) and Bland-Altman analysis.[22] The differences between GSPECT, ECHO and CMRI measurements of LVEF, EDV, and ESV were tested for significance using a t-test for paired samples and $P<0.05$ was considered significant. For linear regression analysis $P<0.01$ was considered significant. Our University Hospital's Scientific and Ethics Committee for Human Clinical Research approved this protocol, and all patients provided informed consent prior to enrollment into the study.

RESULTS

Twenty-one patients (15 male and 6 female, mean age 55±9 years, range 38-74 years) were included in the study. Fifteen patients were hypertensive. One had diabetes mellitus. Five patients had a history of myocardial infarction. No patient was excluded from the study because of the poor image quality of any imaging modality.

Comparison of LVEF Results

The LVEF measured with GSPECT was in the range 23% to 80%, with a mean of 55.9±17.8%. The corresponding values in ECHO were similar: the LVEF was in the range 23% to 77%, with a mean of 55.7±16.4% (Table 1). The linear regression analysis showed very good correlation ($r=0.91$, $P=0.000$) between LVEF assessed with ECHO and with GSPECT. The mean difference in LVEF measured with ECHO and GSPECT was 0.2±7%, with limits of agreement of -13.8% to 14.4% ($P=0.883$, 95% confidence interval, -3.6 to 3.0), as shown by Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. No systematic under- or overestimation of LVEF was found with GSPECT as compared with ECHO.

The LVEF measured with CMRI was in the range 23% to 74%, with a mean of 56.4±15.7% (Table 1). The linear regression analysis showed very good correlation ($r=0.97$, $P=0.000$) between LVEF assessed with ECHO and with CMRI. The mean difference in LVEF measured with ECHO and CMRI was -0.74±4.1%, with limits of agreement of -8.9 to 7.4% ($P=0.412$,

Table 1. Measurement of left ventricular volumes and ejection fraction with the three imaging methods.

	Mean LVEF (%±SD) n:21	Mean EDV (ml±SD) n:21	Mean ESV (ml±SD) n:21
GSPECT	55.9±17.8 (23-80)	109.2±42.4 (46–198)	54.2±41.2 (9–149)
ECHO	55.7±16.4 (23–77)	127.5±42.2 (51.9–249)	59.9±37.6 (14.8–164)
CMRI	56.4±15.7 (23–74)	91.1±38.0 (18.4-151)	41.8±26.9 (6.2-98)

95% confidence interval, -2.6 to 1.1), as shown by Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. There was no systematic under- or overestimation of LVEF with ECHO compared with CMRI. There was also very good correlation (r=0.92, *P*=0.0001) between LVEF assessed with GSPECT and with CMRI. The mean difference in LVEF measured with GSPECT and CMRI was -0.5±7%, with limits of agreement of -14.7 to 13.7% (*P*=0.749, 95% confidence interval, -3.7 to 2.7), as shown by Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. Also no systematic under- or overestimation of LVEF was found with GSPECT compared with CMRI.

In none of the patients was LVEF measured as definitely abnormal (<40%) with one method and as definitely normal (>50%) with other method.

Comparison of EDV Results

The EDV measured with GSPECT was in the range 46 to 198 mL with a mean of 109.2±42.4 mL. The corresponding values in ECHO were similar: the EDV was in the range 51.9-249 mL with a mean of 127.5±42.2 mL (Table 1). The linear regression analysis showed good correlation (r=0.71, *P*=0.000) between EDV assessed with ECHO and with GSPECT. The mean difference in EDV measured with ECHO and GSPECT was 18.3±33.4 mL, with limits of agreement of -48.6 to 85.1 mL (*P*=0.021, 95% confidence interval, 3.0 to 33.5), as shown by means of Bland-Altman analysis. Despite the limits of confidence containing 100% (21/21 samples) of the data points and good correlation between GSPECT and ECHO, EDV was slightly overestimated by ECHO compared with GSPECT.

The EDV measured with CMRI was in the range 18.4-151 mL with a mean of 91.1±38.0 mL (Table 1). The linear regression analysis showed good correlation (r=0.73, *P*=0.000) between EDV assessed with ECHO and CMRI. The mean difference in EDV measured with ECHO and CMRI was 36.4±31.5 mL, with limits of agreement of -26.6 to 99.4 mL (*P*=0.000, 95% confidence interval, 22.1 to 50.7), as shown by Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. The EDV was overestimated by ECHO compared with CMRI. Also there was good correlation (r=0.68, *P*=0.001) between EDV assessed with GSPECT and with CMRI. The mean difference in EDV measured with GSPECT and CMRI was 18.1±32 mL, with limits of agreement of -46.5 to 82.1 mL (*P*=0.018, 95% confidence interval, 3.4 to 32.8), as shown by means of Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. The EDV was slightly, overestimated by GSPECT compared with CMRI.

Comparison of ESV Results

The ESV measured with GSPECT was in the range 9 to 149 mL with a mean of 54.2±41.2 mL. The corresponding values in ECHO were similar: the ESV was in the range 14.8-164 mL with a mean of 59.9±37.6 mL (Table 1). The results of linear regression analysis showed a very good correlation (r=0.86, *P*=0.000) between ESV assessed with ECHO and with GSPECT. The mean difference in ESV measured with ECHO and GSPECT was 5.7±20.8 mL with limits of agreement of -36.0 to 47.3 mL (*P*=0.228, 95% confidence interval, -3.8 to 15.1), as shown by Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. The ESV was not under- or overestimated by GSPECT compared with ECHO.

The ESV measured with CMRI was in the range 6.2 to 98 mL with a mean of 41.8±26.9 mL (Table 1). The results of linear regression analysis showed a very good correlation (r=0.91, *P*=0.000) between ESV assessed with ECHO and with CMRI. The mean difference in ESV measured with ECHO and CMRI was 18.1±17.3 mL with limits of agreement of -16.5 to 52.7 mL (*P*=0.000, 95% confidence interval, 10.2 to 25.9), as shown by means of Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data point. The ESV was underestimated by CMRI compared with ECHO. Also there was a very good correlation (r=0.91, P=0.000) between ESV assessed with GSPECT and with CMRI. The mean difference in ESV measured with GSPECT and CMRI was 12.4±19.9 mL, with limits of agreement of -27.4 to 52.2 mL (P=0.010, 95% confidence interval, 3.3 to 21.5), as shown by means of Bland-Altman analysis. These limits of confidence contained 95.2% (20/21 samples) of the data points. The ESV was underestimated by CMRI compared with GSPECT.

DISCUSSION

Left ventricular function and volumes have major diagnostic and prognostic importance in patients with various cardiac diseases.[1] Nowadays several noninvasive techniques are available for this purpose, including ECHO, CMRI, RNV and GSPECT. In recent years all of these imaging techniques have become more available, and clinicians could be faced with LVEF and LV volume results obtained with various imaging techniques during a long follow-up period. Therefore, cardiologists need to know the exact correlation and agreement between these techniques. Another concern is whether measurements of LV volume and ejection fraction derived from different techniques could be used interchangeably. In contrast to most studies, which included only two imaging modalities (GSPECT vs. ECHO or CMRI; ECHO vs. GSPECT or CMRI) we performed three imaging methods in the same group of patients. The present study is, to our knowledge, only the second one to compare left ventricular functions (LVEF, EDV and ESV) derived from GSPECT, CMRI and ECHO in the same group of patients. In the first study, Yamamuro et al[23] performed multi-detector row CT and magnetic resonance imaging in 50 patients, two-dimensional ECHO in 41 patients and GSPECT in 27 patients. They found that the standard deviation of the EF difference between multi-detector row CT and MR imaging was significantly less than that between echocardiography and MR imaging (P<0.001) or that between GSPECT and MR imaging (P<0.001). According to previous studies that compared GSPECT and ECHO there was very good agreement between LVEF, EDV and ESV values.[1,5-7,9-11,23] Fleming found a high correlation (r=0.76) between resting echocardiographic EFs and SPECT resting gated sestamibi images in patients with single-vessel disease, and a moderate correlation (r=0.68 and r=0.68) in patients with 2- and 3-vessel disease, respectively.[5] In a recently published study, we compared left ventricular function and volumes of GSPECT and ECHO in patients with dilated cardiomyopathy. We found good correlations for the assessment of LVEF, EDV and ESV (r=0.72, r=0.71 and r=0.71, respectively).[9] In the present study, when we compared the results of GSPECT and ECHO, the values for LVEF, EDV and ESV correlated strongly (r=0.91, r=0.81, r=0.71, respectively). Also no systematic under- or overestimation of LVEF and ESV values was found with GSPECT as compared with ECHO according to Bland-Altman plots. However, EDV was slightly overestimated by ECHO compared with GSPECT.

A number of studies have compared GSPECT and CMRI.[4,8,12-19] Thorley et al. compared GSPECT with CMRI measurements of LVEF and EDV in 50 patients and found a good correlation (r=0.82 and r=0.90).[13] In another study, Bavelaar-Croon and colleagues also found a good correlation for LVEF, EDV and ESV (r=0.85, r=0.94, r=0.95, respectively).[14] In our study, LVEF, EDV and ESV results of GSPECT were also correlated very well with CMRI results (r=0.92, r=0.68, r=0.91, respectively). LVEF was not under-or overestimated by GSPECT compared with CMRI. But, EDV and ESV were slightly underestimated by CMRI compared with GSPECT. Interestingly, most previous studies have reported that volumes were underestimated by GSPECT compared with CMRI.[16,17,24] However, some studies showed results similar to ours.[8,15,18] Faber et al reported that both Quantitative Gated SPECT (QGS) and Emory Cardiac Toolbox (ECTb) had given EDV and ESV 20% to 30% larger than the MR measurements.[8] Similarly, Vaduganathan et al found volumes to be larger when computed with GSPECT than with CMRI.[15] Because of high spatial resolution, excluding papillary muscles and trabeculations from volumes in CMRI was easier than in either GSPECT and ECHO. In our study, to exclude major vascular structures and valves from ventricular volume slices of CMRI were minimally repositioned to midventricular region at the base of the heart. So, inclusion or exclusion of the most basal slice, which consists of parts of LV myocardium, outflow tract, and left atrium, could be the main reason for the difference between previous studies and the present study. In addition, the frame numbers per cardiac cycle were different in CMRI and GSPECT (16 vs. 8 frames for CMRI and GSPECT, respectively). We used 8 frames for GSPECT images to obtain sufficient count statistics. This could be the technical reason for the conflict in volume results.

Direct comparison of CMRI and ECHO was made using different protocols and imaging techniques, in some previous studies.[3,23,24-28] Hoffmann et al, in a multi-centre study, assessed the agreement of LVEF derived from cineventriculography, .cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography in 120 patients. They reported that the correlation for EF between MRI and unenhanced echocardiography was 0.60.[3] In most of those studies that compared CMRI and ECHO, measurements of CMRI were larger than ECHO results.[3,25-28] In the present study, LVEF, EDV and ESV values from CMRI and ECHO correlated very well. While LVEF was not under-or overestimated by CMRI compared with ECHO, the values of EDV and ESV were underestimated. We think the reasons for the difference between CMRI and GSPECT results (exclusion of basal portions of left ventricle and high spatial resolution of CMRI) also account for the difference between ECHO and CMRI results.

In addition to very good correlations and agreements between the LVEF values for these three imaging modalities, in none of the patients was LVEF measured as definitely abnormal (<40%) with one method and as definitely normal (>50%) with the other method. This result is in agreement with the study by Bavelaar-Croon and colleagues.[14] Thus, LVEF results obtained from any of these three imaging modalities could be used interchangeably.

In conclusion, we found overall very good correlations and agreements between LVEF derived from GSPECT, CMRI and ECHO as shown both linear regression and Bland-Altman analysis. Even though we found good correlations between EDV and ESV values derived from all of these imaging modalities, agreemens between these results were not as good as between LVEF results. Therefore, care should be taken in comparing LV volumes derived from these three imaging methods.

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original article

Predictors of obstructive sleep apnea in snorers

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BACKGROUND: Snoring is a common problem that poses a high risk for obstructive sleep apnea (OSA). We studied the contribution of risk factors for OSA in snorers referred for full-night polysomnography (PSG).
METHODS: A questionnaire was administered to subjects referred for PSG in the period from April 2002 to March 2005.
RESULTS: There were 191 (84%) snorers identified by 227 PSG studies. They had a mean age of 48.1±9.8 years, (age range, 23-73 years) and 78.5% were males. OSA as indicated by a respiratory disturbance index (RDI) of >5 events/hour was seen in 126 (66%) subjects. In males, 72.7% had OSA, with a mean RDI of 43.0±26 events/hour, versus 39% with OSA in females with a mean RDI of 27.8±26.5 events/hour ($P<0.001$). The OSA group had a higher mean Epworth Sleepiness Scale (ESS) ($P<0.001$), a larger mean neck circumference ($P<0.01$), an increased mean age ($P<0.05$), and more witnessed apneas ($P<0.001$) but not choking ($P=0.096$). The mean increase in body mass index was linked to OSA only in females ($P<0.05$) but not in the overall study ($P=0.507$). Multivariate analysis showed that ESS, male gender, and a history of witnessed apnea were associated with OSA, while controlling for obesity, large neck circumference, age, and history of choking.
CONCLUSION: In screening snorers for PSG, male gender, ESS and a history of witnessed apneas were the most important predictors of OSA, but other factors should be considered in referring snorers for PSG. In males, obesity did not contribute to the risk of OSA in our study population.

Snoring is an important health issue that is reported to occur in 20% to 60% of the adult population.[1] It is the most common symptom of OSA, a condition associated with disturbed sleep and excessive daytime sleepiness that is seen in at least 4% of men and 2% of women 30 to 60 years of age.[2] By itself, however, snoring does not definitely imply the presence of OSA.[3] A quick and reliable screening test would enable clinicians to detect the possibility of OSA during initial office visits and then decide which patients are at high risk and urgently in need of polysomnography (PSG). The Epworth sleepiness score (ESS) has been extensively used as an important parameter in predicting OSA and screening subjects before referral for PSG. Other factors considered are male gender, older age (>50 years),[4] body mass index (≥30),[5] neck circumference (≥17 inches in males and ≥16 inches in females),[6] history of apnea witnessed by the bedroom partner, and awakening with choking.[8] In this cross-sectional observational prospective study we estimated the frequency of OSA in snorers in our center and present our experience in assessing the factors associated with the polysomnographic diagnosis of OSA in this group.

PATIENTS AND METHODS

A pre-designed database with the demographic data, clinical details, symptom-specific questions for diagnosis of OSA. A questionnaire with ESS was administered to all patients presenting to the snoring clinic at Hamad General Hospital, a tertiary hospital in the state of Qatar.

A total of 227 adult subjects underwent PSG from April 2002 to March 2005 for different indications excluding pediatric cases. In this study, we recruited only adult subjects who were referred with a main complaint of snoring to rule out OSA. A total of 191 (84%) PSG studies met the following inclusion criteria: 1) age >18 years old; 2) snoring that was reported as frequent on most days of the week; 3) no previous sleep study done; 4) demographic data and Epworth sleepiness score completed; 5) upper airway obstruction excluded by ENT specialist; 6) a full night PSG study with a total sleep time >6 hours. Narcoleptic patients, significant periodic limb movement index, predominantly central sleep apnea, and multiple sleep latency studies were excluded from the analysis.

A sleep study questionnaire that includes ESS was completed in the clinic and rechecked with the patient on the night of the sleep study. Sleepiness was defined as the score on the ESS, a well-validated eight item questionnaire that asks the subject to rate his or her likelihood of falling asleep in a variety of commonly encountered situations. Possible total score range from 0 (no sleepiness) to 24 (the most sleepy). A score of 11 or higher was considered to represent an abnormal degree of daytime sleepiness.[9] For apneas and choking, either subjects or bedroom partners were asked about episodes in which the patient stops breathing indicating apnea and then gives a loud gasp or snort when aroused by the apnea to describe the choking sensation.

Patients had an overnight PSG using the Alice 4 Resporonics system. The PSG consisted of 14 channel continuous polygraphic recording from surface leads for 2 electroencephalography, 2 electro-oculography, chin electromyography, electrocardiography, sensors for nasal airflow (thermister), tracheal sounds (microphone), thoracic and abdominal respiratory effort (piezo-electric), finger pulse oximeter, leg movements, body position and light. A trained physician scored sleep stages in 30-second epochs according to standard criteria. An apnea was defined as complete airflow cessation of more than 10 seconds. A hypopnea was defined as a reduction in airflow of >50% for more than 10 seconds that led to a 4% or greater oxyhemoglobin desaturation. Patients were grouped by their total respiratory disturbance index (RDI) score at PSG. These groups were RDI of 0 to 4.9 considered as normal, and those with RDI ≥5 considered abnormal and having OSA. The abnormal RDI group were subdivided to: RDI 5 to 14.9 (mild OSA), 15 to 29.9 (moderate OSA), and >30 (severe OSA).

The data are presented as means±SD for continuous variables and as percentages for categorical variables. Comparison between the groups was done with the t test for continuous variables and chi-square test for discrete variables. ANOVA test was used to study the average increase in ESS, BMI, NC and age in the different OSA severity. Multivariate logistic regression models were applied to identify the overall and independent factors in relation to OSA. The factors considered were sex, age ≥50 years old, ESS ≥11, and BMI ≥30 and a cut point for NC ≥ was chosen at 43 cm, history of witnessed apneas and awakening with choking. A P value of <0.05 was considered as statistically significant. All analysis was done with SPSS (Chicago, IL) version 10.0 for Windows.

RESULTS

A total of 227 PSGs were performed in the period between April 2002 to March 2005 for adult patients. Snorers comprised 191 (84%) subjects, including 150 men (78.5%) and 41 women (21.5%) who met the inclusion criteria and formed the basis for this analysis. The mean age was 48.1±9.8 years (age range, 23-73 years). Qatari subjects constituted 75 participants (39.3%) while other nationalities formed 116 participants (60.7%). The average sleep time was 6.33±0.20 hours. The characteristics of the two groups of normal RDI and abnormal RDI in relation to gender, age, neck circumference, BMI and ESS are shown in Table 1. Table 2 shows the significance of the relationship of age, NC, BMI, ESS for different categories of RDI.

OSA as indicated by an RDI ≥5 was seen in 126 of 191 (66%), with a mean RDI of 40.9±26.5 events/hour (Table 1). OSA was seen more in men than women (P<0.001). OSA was seen more in non-Qatari subjects (84 of 116, 72.4%) versus [38 out of 75 (52%)] in Qatari subjects (P< 0.05). Arousal index was higher in the OSA group versus the normal group (P<0.001).

Subjects were divided into four groups based on RDI: 65 (34%) subjects were considered normal (RDI <5), 30 (16.9%) subjects had mild OSA (RDI 5 to 14.9), 24 (12.5%) subjects had moderate OSA (RDI 15 to 29.9), and 72 (37.5%) subjects had severe OSA (RDI >30). The OSA group had a higher mean age of 49.1±9.4 years compared to 46.2±10.2 years in the normal group (P<0.05). Females had a non-significantly higher mean age of 51.8±8.2 years compared to 48.7±9.4 years in males (P=0.195). There were no statistically significant differences in the mean age comparing the different OSA categories.

The OSA group had a significantly higher mean NC compared to the normal group (P<0.05). In the OSA group, males had a higher mean NC compared to females (P<0.05). Only the group with severe OSA showed a statistically significant difference in the mean NC (P<0.001), comparing the different OSA categories.

The percentage of obesity was 69.8% in the group with OSA, and 67.7% in the normal group. The OSA group had a mean BMI of 34.3±7.5 kg/m^2 compared to 33.6±7.0 kg/m^2 in the normal group (P=0.507). Females with OSA had a significantly higher BMI of 42.1±8.9 kg/m^2 compared to BMI of 33.2±6.5 kg/m^2

in males ($P<0.001$). There were no statistically significant differences in the mean BMI in the different OSA categories.

Witnessed apneas were reported in 85 of 126 (67.5%) subjects in the group with OSA versus 27 out of 65 (41.5%) subjects in the normal group ($P<0.01$). They were reported in 41.5% in the normal group, 63.3% in the mild OSA, 54.2% in the moderate OSA, with the group of severe OSA statistically showing the highest frequency of apneas in 73.6% of the subjects ($P<0.01$). In males with OSA, apneas were noticed in 76 out of 109 (69.7%) subjects versus 9 of 17 (52.9%) females ($P=0.170$).

Awakening with choking was seen in 76 of 126 (60.3%) subjects in the group of OSA versus 31 of 65 (47.7%) subjects in the normal group. ($P=0.096$). It was reported in 47.7% in the normal group, 46.7% in the mild OSA, 54.2% in the moderate OSA group, with the group of severe OSA showing the highest frequency in 68.1% of subjects ($P=0.067$). In males with OSA, choking was reported in 71 of 109 (65.1%) subjects versus 5 of 17 (29.4%) females ($P<0.01$).

The OSA group was associated with a higher mean ESS compared to the normal group ($P<0.001$). Because of the importance of the ESS in referring subjects for PSG, it was further assessed in relation to the four categories of RDI severity. A statistically significant linear increase in mean ESS score was present across all categories of RDI ($P<0.001$) (Table 2). The prevalence of sleepiness as indicated by ESS score ≥11 was seen in 89 of 191 (46.6%) subjects ($P<0.001$). OSA was seen in 74 (83.1%) subjects with sleepiness. In the group with low ESS <11, there were 102 (53.4%) subjects, with 52 (51.0%) subjects with OSA. The frequency of excessive sleepiness at different degrees of RDI were 16.7% in normal group, 14.4% in mild OSA, 12.2% in moderate OSA, 56.7% in severe OSA and consequently, the group with severe OSA showed statistically the highest prevalence ($P<0.001$).

In a multivariate logistic regression analysis (Table 3), sex, age >50 years old, BMI ≥30 kg/m^2, NC >43 cm, ESS ≥11, a history of witnessed apneas and awakening with choking were analyzed. ESS ≥11, male gender, and witnessed apneas were the most important predictors of obstructive sleep apnea.

DISCUSSION

OSA is a common sleep disorder characterized by recurrent episodes of apnea during sleep associated with snoring. Large-scale epidemiological studies have estimated that 4% of males and 2% of females are affected by symptomatic OSAS.[2,10] Researchers estimate that

Table 1. Characteristics of 160 subjects with snoring divided into those with OSA (RDI ≥5) and those without OSA (RDI <5). (Data expressed as mean±SD).

Variable	RDI positive n=126*	RDI negative n=65 *	*P* value
Age* (years)	49.1±9.4	46.2±10.2	0.043
Male*	48.6±9.5	43.7±9.3	0.005
Females	50.3±10.7	51.8±8.2	0.609
BMI (30 kg/m^2)	34.3±7.5	33.6±7.0	0.507
Male	33.2±6.5	31.8±5.8	0.208
Female*	42.1±8.9	36.1±8.0	0.028
NC* (cm)	41.6±3.2	40.0 ±3.6	0.002
Male	41.9±3.0	41.3±3.0	0.241
Female*	39.5±3.5	37.5±3.5	0.069
ESS *	11.6±4.6	7.2±4.2	0.0001
Male*	11.6±4.5	6.7±4.3	0.0001
Female*	10.9±5.0	7.9±4.3	0.044
RDI* (events/hr)	40.9±26.5	1.5±1.3	0.0001
Male* (n=150)	43.0±26.0 (n=109)	1.5 ±1.3) (n=41)	0.0001
Female*(n=41)	27.8±26.5 (17)	1.3 ±1.2) (n=24)	0.001
Arousal Index*	37.8±27.2	15.1±12.3	0.0001

Definitions of abbreviations: BMI: body mass index, NC: neck circumference, RDI: Respiratory disturbance index, ESS: Epworth sleepiness score

* T- test: $P<0.05$ comparing the groups of RDI ≥5 (OSA) versus RDI <5.

Table 2. Relation of associated factors to different categories of RDI (Data expressed as mean±SD).

Characteristic	Normal RDI<5	Mild OSA	Moderate OSA	Severe OSA	*P* value
Age (years)	46.1±10.3	47.8±9.5	49.4±6.5	49.8±10.1	0.171
BMI (kg/m^2)	33.6±7.0	35±7.4	33.8±9.0	34.3±7.0	0.759
NC* (cm)	39.8±3.6	41.2±3.2	40.3±2.4	42.2±3.4	0.001
ESS*	7.2±4.3	9.6±5.0	10.3±4.6	12.6±4.1	0.0001

Definitions of abbreviations: RDI: respiratory disturbance index, BMI: Body mass index, NC: Neck circumference, ESS: Epworth sleepiness score

*(ANOVA test) $P< 0.05$ for differences between groups.

Table 3. Predictors of OSA in snorers.

Characteristic	Odds ratio (95% CI)	*P* value
Age ≥50 years	1.84 (0.90-3.75)	0.093
Sex*	3.44 (1.57-7.55)	0.002
BMI ≥30 kg/m2	0.98 (0.45-2.18)	0.974
NC ≥43 cm	1.02 (0.49-2.33)	0.878
ESS≥ 11*	4.35 (2.13-8.90)	000
Witnessed apnea*	2.09 (1.06-4.10)	0.033
Choking	1.12 (0.54-2.33)	0.769

Definitions of abbreviations: BMI: Body mass index, NC: neck circumference, ESS: Epworth sleepiness score

*Multivariate Logistic regression analysis: $P< 0.05$

82% of men and 93% of women with moderate-to-severe OSAS have not been clinically detected or diagnosed.[11] The delay in diagnosis and treatment has led to prolonged morbidity.[12] Furthermore, snoring is a common complaint in patients with OSAS, but by itself does not imply OSAS. Those patients face considerable delays before receiving appropriate treatment for snoring or for OSAS. The current practice guidelines advise referring patients who present with snoring and daytime sleepiness to specialist sleep services for comprehensive investigation using PSG.[1] In our center, subjects with snoring are mostly referred from snoring clinics for PSG, based on their sleepiness score and other risk factors like obesity, increased neck circumference or older age. But in some circumstances, even in the absence of obvious risk factors, PSG is performed based on the physician desire to rule out OSA as a pre-operative assessment in subjects who would undergo surgical treatment for snoring. Qatari subjects are more likely to fall in this category, which may in part explain the lower prevalence of OSA in Qatari snorers in our study.

The frequency of PSG diagnosed OSA indicated by an RDI ≥ 5 in this selected population of snorers was 72.4%. A significant OSA as indicated by an RDI ≥ 15 was seen in 50%. The study has shown the expected relation of OSA to male gender, increasing age, BMI, NC, and ESS, although it did not reach statistical significance for BMI.

OSA is expected to have a male to female ratio of 8 to 1.[13] The reason for the lower prevalence of OSA in women than in men is not fully understood. The influence of female sex hormones has been considered, but their exact role in OSA is not clear. Although initial reports emphasized the high prevalence of morbid obesity in women with OSA, as is evident in our study where only in females was obesity related to OSA, reflecting the significantly higher mean BMI compared to males. More recent studies have described OSA in women without significant obesity. The greater central body fat distribution and larger neck dimensions of men may account for some but not all of the sex differences found in OSA prevalence.[14]

Similar to other studies; our study has shown an association between OSA and increased age.[13] Age showed a linear increase across all severity of OSA that did not reach statistical significance.

In considering obesity, approximately 60% to 70% of patients with OSA are obese and a close association between BMI and OSA in adults has been noted in different studies.[15,16] Obesity has been shown to be directly related to the severity of the disease.[17] Contrary to studies that have shown less prevalence of obesity in Asian population,[18] obesity was highly prevalent in the snorers referred for PSG in our center. However, unexpectedly it was not associated with an increased risk or severity of OSA either independently or when controlling for ESS, NC, age or sex. Some studies suggest that OSA may differ by race, reflecting the interplay of various risk factors in different populations, because of differences in environmental and genetic factors.[19] It may be proposed that other factors should be considered before referring obese snorers for PSG in our center.

Increased neck circumference showed an independently linear association to RDI in our study, as is shown in other studies.[20,21] But only the severe OSA group showed a significantly higher mean NC. The effect of NC was not significant when controlling for other factors in the study.

In considering the symptoms of OSA, different studies report conflicting results, with sleepiness and apneas being the most significant while choking and other OSAS symptoms showed less correlation.[22] In our study apnea was witnessed more frequently in OSA group ($P<0.01$), which is expected in a disorder that is commonly reported by the bedroom partner witnessing the loud snoring and periods of complete cessation of breathing in the subject. Choking was reported more frequently in the OSA group but did not reach statistical significance. This may be partly explained by the fact that most of our subjects respond individually to our questionnaire, and choking may be unrecognized with patients usually unaware of the occurrence of "micro-arousals".

ESS was one of the main factors examined extensively in subjects referred for sleep studies with primary complaints of snoring. Excessive daytime sleepiness (EDS) is a common condition, reported by 5% to 12% of adult subjects in population surveys.[23] EDS has been linked to the OSAS diagnosis in middle-aged populations with mildly elevated RDI. The ESS is commonly used by clinicians to quantify the degree of daytime sleepiness. It measures propensity for daytime sleepiness in adults and at a cutoff score of ≥11, this measure has 94% sensitivity and 100% specificity. While this questionnaire is not specifically diagnostic for OSA, it is a useful indicator of general sleep disorder.[24] However, since daytime sleepiness can result from a number of factors, some investigators have shown that this score may be unreliable in confirming the presence of OSA.[25]

ESS sensitivity ranges from 60% to 65% and specificity ranges from 77% to 80% in predicting OSA.[26,27] The mean ESS in the OSA group was higher than the normal group and progressively increased among all groups of OSA severity in a manner that was highly statistically significant ($P=<0.001$). The prevalence of excessive daytime sleepiness was noted to be 16.7% in the normal RDI group, which is somewhat similar to the prevalence of 12% to 20% noted in population surveys.[2] Other studies have reported a 21% to 25% prevalence of excessive sleepiness with (ESS ≥11) in subjects with an RDI<5.[23,28]

Young and colleagues 2 have shown that snorers with an RDI <5 are more likely than non-snorers with RDI <5 to report excessive sleepiness. In those patients upper airway resistance syndrome is an expected problem, where repetitive arousals occur in response to partial collapse of the upper airway, despite minimal if any detectable decrease in airflow. Conversely, a high percentage of the population experiences nocturnal apneas and hypopneas without reporting excessive sleepiness, as shown in 26.7% of subjects in our study (Table 3). Furthermore, some subjects with severe OSA may report only a minimal degree of daytime sleepiness.

In patients with OSA, sleep fragmentation by repeated arousals in response to apneas and hypopneas is the apparent cause of excessive sleepiness. Our study has shown significantly higher arousal index in the group of abnormal RDI as compared to subjects with normal RDI ($P<0.001$). It is likely that arousal from sleep in response to respiratory events explains the association of RDI with sleepiness in our subjects.

Some patients who are seen in the snoring clinic in our hospital are planned for possible surgical procedures as a treatment for snoring if OSA is ruled out. The association with OSA should be recognized preoperatively to avoid the immediate post- operative risk in those patients. Depending on one clinical parameter for referring patients for PSG like ESS carries the risk of missing a significant number of cases, and may lead to prolonged morbidity and health consequences. Some studies have shown that a rank order of symptoms and clinical indicators may help in identifying the cases, which needs urgent evaluation by PSG.[1,29,30] But the possibility of missing cases with OSA even in asymptomatic snorers may still exist, because of the lack of simple measures that help in early referral for PSG.

Portable screening PSG devices are of great help in decreasing the burden on the limited availability of sleep laboratories, and can be used in screening subjects at risk of OSA like snorers, even if clinical indicators are not suggestive of presence of significant OSA.

Our study is limited by the presence of an element of personal clinical judgment in referring subjects for PSG. Yet this pre-selection of the sample has allowed us to identify those factors of importance that may encourage us to review our strategies for referral to a busy PSG unit, e.g. by introducing portable PSG devices as a screening test in our center. The study also presents the polysomnographic diagnosis of OSA, which may not be the actual reflection of the magnitude of OSAS in this study group. The contribution of different risk factors on the severity of OSA was evaluated, but other studies are needed to present those and other factors that are more predictors of symptomatic OSA i.e. OSAS. We did not present our data regarding the association of OSA to other comorbid conditions because those were not the primary concern in referring those subjects and are a matter of detailed discussion in other studies.

In conclusion, snoring is an important risk factor for OSA. Male gender, older age, increased neck circumference and ESS, and a history of witnessed apneas are independent predictors. BMI is an important predictor in females who are morbidly obese but not in male subjects in our center. In a multivariate logistic regression analysis, male gender, sleepiness evaluated by ESS, and witnessed apneas were the most important factors predicting OSA in our study sample. Nevertheless, other factors are to be considered in referring subjects for PSG in high-risk groups like snorers, to avoid the possibility of missing cases in this disabling problem.

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original article

Bone mineral density in children with systemic lupus erythematosus and juvenile rheumatoid arthritis

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BACKGROUND: Although there is increasing interest in bone metabolism in patients with rheumatic disorders, few data exist on bone mineral density (BMD) in children with rheumatic disorders or on the association of BMD with disease-related variables. We determined BMD in Iranian children with systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA) to evaluate the relationship between disease-related variables and BMD.

PATIENTS AND METHODS: Twenty patients (13 girls and 7 boys) with SLE (n=15) and JRA (n=5) with a mean age of 13.10±3.29 years (range, 6-17 years), attending a pediatric rheumatology clinic and 20 healthy controls (matched for age and sex with each patient) were enrolled in a cross-sectional study between 2001 and 2003. BMD (g/cm^2) of the femoral neck (BMD-F) and lumbar vertebrae (BMD-L) were measured by dual energy X-ray absorptiometry (DEXA). The correlation between BMD and cumulative dose of steroids, daily dose of steroid, disease duration, disease activity, height, weight, and age was investigated.

RESULTS: BMD in the patients (BMD-F=0.72±0.15, BMD-L=0.70±0.19) was significantly lower than controls (BMD-F=0.95±0.17, BMD-L=0.98±0.20, $P<0.001$). The severity of decreased BMD was more prominent in lumbar vertebrae than the femoral neck ($P=$ 0.04). None of the variables were consistently related to a decrease in BMD.

CONCLUSION: BMD was significantly lower in patients compared with controls. It was more prominent in lumbar vertebrae (trabecular bone). Although cumulative dose of steroids and disease duration appeared to have some influence on BMD, none were independently correlated with BMD.

Osteoporosis is characterized by loss of both bone mass and microarchitectural integrity, resulting in an increased risk of fractures with associated morbidity and mortality.[1] Increasing interest has focused on bone metabolism in patients with rheumatic disorders. In adults with rheumatic disorders a number of risk factors for development of osteoporosis have been described, including disease duration and severity, diet, level of physical activity, past corticosteroid treatment, and reduced exposure to sunlight due to photosensitivity.[2,3] Only a few such studies have addressed childhood-onset rheumatic disorders, particularly systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA).[4-8]

Dual-energy X-ray absorptiometry (DEXA) has become a standard technique for the measurement of bone mineral density (BMD) of the lumbar spine, femur, forearm, and whole body, due to its low radiation dosage, ease of use, rapidity, accuracy, precision, and reproducibility under controlled circumstances.[9,10] We studied BMD by DEXA in a cohort of Iranian children and adolescents with SLE and JRA and compared it with that in healthy age- and sex- matched controls. We also investigated the relationship between several disease-related variables and BMD.

METHODS

Twenty patients (13 girls and 7 boys) with SLE (15) and JRA (5) with mean age of 13.10±3.29 years (range, 6-17 years), attending the pediatric rheumatology clinic of Motahari clinic at Shiraz, Iran, were enrolled in a cross-sectional study between 2001 and 2003. The inclusion criteria were disease onset before the age of 17, a minimum disease duration of 6 months, and the presence of at least four of the American College of Rheumatology (ACR) criteria for classification of SLE.[11] In 5 patients the diagnosis of JRA was based on the ACR criteria for diagnosis of JRA.[12] At the time of this study all patients had been receiving steroids, calcium and vitamin D during the past 6 months. Disease duration was defined as the period of time from the diagnosis of disease based on the appearance of initial clinical symptoms clearly attributable to the disease until the time of the study. Twenty healthy controls (matched for age and sex with each patient) were selected randomly from the schools located in Shiraz. All participants were ethnic Iranians and ate typical Iranian food. Informed consent was obtained from the patients, controls, and their parents. This study was approved by our university ethics committee.

A clinical examination was performed on all of the patients and controls. A questionnaire was completed based on the information obtained from the patients' medical records and by interviewing all of the participants or their parents. Collected data included age, sex, height, weight, food and nutrient intake, cumulative corticosteroid dose, mean daily corticosteroid dose at the time of study, and disease duration. A self-reported health status questionnaire of physical activity and pain perception was also completed by the patients. In patients with SLE and JRA, disease activity was measured by the SLE Disease Activity Index (SLEDAI)[13] and ACR core set.[14]

BMD (g/cm^2) of the femoral neck (BMD-F) and the second through fourth lumbar vertebrae (BMD-L) were measured with DEXA equipment (Lunar DPX-IQ, USA). At present, Iranian reference values for bone mass measurement in children are not available. We therefore chose to compare BMD of our patients with the control group.

The Wilcoxon Signed Ranks Test was used to compare the BMD of patients and controls and to compare BMD-F with BMD-L. Correlation between reduction in BMD (BMD in controls – BMD in patients) at femoral neck and lumbar vertebrae and disease duration, amount of steroid, disease activity, and weight and height of patients, was determined by Spearman's method, and then potential risk factors were entered into multiple linear regression analysis. Data are expressed as mean±SD unless otherwise stated. *P*-values less than or equal to 0.05 were considered significant. All statistical analysis was performed using SPSS software.

RESULTS

The study population consisted of 15 patients with childhood-onset SLE and 5 patients with JRA, and 20 healthy controls, who were individually matched for age and sex (Table 1). Mean height and weight of patients was significantly lower than controls. BMD of the patients (BMD-F=0.72±0.15 g/cm^2, BMD-L=0.70±0.19 g/cm^2) was significantly lower than controls (BMD-F=0.95±0.17 g/cm^2, BMD-L= 0.98±0.20 g/cm^2, $P<0.001$). The severity of decreased BMD was more prominent in lumbar vertebrae than the femoral neck ($P= 0.04$). The mean disease activity index for SLE patients (SLEDAI) was 9±6.98 and for JRA patients was 93.8±55.47 at time of examination.

On the basis of SLEDAI scores, five patients had mild disease activity (SLEDAI=1-5), five patients had moderate activity (SLEDAI=6-10), four patients had high activity (SLEDAI=11-19), and one patient had very high activity (SLEDA= or >20) (Table 2).[15] Active

Table 1. Characteristics of patients and healthy controls.

Characteristic	Patients (n=20)	Controls (n=20)	*P* value
Female/male	13/7	13/7	>0.05
Age, years	13.10±3.29	13.10±3.29	>0.05
Weight, kg	38.35±15.63	49.2±14.37	<0.01
Height, cm	143±17.59	156.5±15.09	<0.01
Disease duration, years	2.65±2.18	-	NA
Cumulative dose of steroids, mg/kg	273±379.40	-	NA
Daily corticosteroid dose, mg	6.62±3.17	-	NA
BMD, Spine, g/cm^2	0.70±0.19	0.98±0.20	<0.001
BMD, Femoral neck, g/cm^2	0.72±0.15	0.95±0.17	<0.001

NA: Not Applicable

JRA was defined in all of our JRA patients as their score was greater than 20 based on ACR core set.[14] There was no relationship between disease activity and BMD.

Potential risk factors for low BMD were cumulative dose of steroid, disease duration, disease activity, daily dose of steroid at the time of BMD evaluation, height, weight, and age. Although cumulative dose of steroids and disease duration were considered correlated (Spearman's method) with the decrease in BMD, using multiple linear regression analysis, this association did not reach significance. Therefore no disease-related variables were identified as independent predictors of BMD.

DISCUSSION

The relationship between chronic childhood rheumatic disorders and BMD has been investigated in a relatively small number of studies.[4-8] Our results confirm that decreased bone density is a common problem in these patients. To our knowledge, the present study is the first to report BMD in Iranian children with rheumatic disorders and to describe the risk factors associated with decreased bone density in this population.

In the current study we found no factors that were consistently related to the decrease in BMD. Although several researchers investigated the role of such factors as disease activity, disease duration, and corticosteroid use in the pathogenesis of osteoporosis in adult patients with rheumatic disorders,[2,3,16] similar investigations have led to still more controversial results in children.

Alsufyani et al[5] in a study conducted on 36 child patients (25 SLE) found a reduced bone density in patients with rheumatic disorders but no factors were associated with this decrease in BMD. We reached the same results. Head et al[7] reported normal BMD in African-American children with JRA who had not previously been treated with corticosteroids. A positive correlation was suggested between severity of osteopenia and total amount of steroid used by patients with JRA in the course of their illness,[17] also osteopenia was more common in more prolonged JRA.[18]

Lilleby et al[6] in a survey carried out on 70 Norwegian children with SLE and 70 healthy controls found cumulative dose of corticosteroids to be an important variable in explaining decreased bone mass, also male sex was related to the decrease in lumbar spine bone mass. Comparing the values of BMD, it is notable that values in our children are significantly lower compared with Norwegian children, probably based on nutritional and ethnic variations (Table 3). Both studies are comparable regarding age range, corticosteroid dose, and DEXA equipment.

Table 2. BMD of femoral neck and spine, disease activity index, and Tanner stage of children with systemic lupus erythematosus and juvenile rheumatoid arthritis.

	Femoral neck (g/cm²)	Spine (g/cm²)	Disease activity index	Tanner stage
SLE patients				
1	0.653	0.602	1	IV
2	0.796	0.801	1	IV
3	1.015	0.953	1	IV
4	0.986	1.063	1	III
5	0.723	0.844	2	IV
6	0.541	0.574	8	I
7	0.694	0.588	8	III
8	0.896	0.893	8	IV
9	0.858	1.037	8	III
10	0.77	0.604	10	II
11	0.753	0.714	15	III
12	0.792	0.827	15	III
13	0.715	0.693	18	I
14	0.833	0.856	19	III
15	0.733	0.699	20	II
JRA patients				
1	0.568	0.492	21	I
2	0.593	0.581	63	II
3	0.709	0.452	89	I
4	0.525	0.44	139	III
5	0.423	0.375	157	I

The impact of puberty on BMD is described in healthy boys and girls.[19,20] De Schepper et al[20] proposed that the total increase in BMD during puberty was higher than that during the proceeding 10 years, representing a 40% increase in BMD during puberty. They also reported that pubertal stage IV is responsible for the most important increase in lumbar spine BMD in both sexes. Van Coeverden et al[21] reported an increase of up to 60% in bone mass at all skeletal sites between Tanner stages II and IV. Our results do not support the association between BMD and pubertal stage in children with SLE and JRA; similar results were obtained in another study carried out on children with SLE.[5]

It is perhaps interesting that we found no consistent relationship between BMD and disease related variables; the most probable explanation is that the relatively small number of patients provided inadequate power

Table 3. BMD comparison between Iranian and Norwegian children.

BMD, g/cm²	Patients			Controls		
	Iranian	Norwegian	*P* value	Iranian	Norwegian	*P* value
Spine	0.70±0.19	1.03±0.20	< 0.001	0.98±0.20	1.16±0.19	0.005
Femoral neck	0.72±0.15	0.95±0.18	< 0.001	0.95±0.17	1.05±0.16	0.06

to reveal the association of any individual factor with bone density.

It is postulated that obtaining the bone density value without some means of comparing it to a reference or normal range is of limited use.[10] Z scores are values that relate bone density scores to normal values matched for age, sex, and ethnicity.[5] According to the literature,[22] a Z score derived from the manufacturer's normal data are probably not appropriate for use in other populations. As no normative data were available for Iranian children to match for ethnicity, we did not calculate Z scores in our study. We showed that decreased BMD in chronic rheumatologic patients is more prominent in trabecular bones such as vertebra. The same results were achieved by other researchers.[23]

In conclusion, we observed lower bone mass in the lumbar spine and femoral neck in patients with childhood-onset SLE and JRA compared with healthy controls. These results should alert clinicians to the potentially high risk for the development of osteoporosis later in life in these patients. It is important to highlight that whereas weight and height may normalize over time with disease control, impaired peak bone mass may never be corrected.[24] Therefore, efforts should be made to reduce steroid to the lowest possible maintenance dose, and to stimulate bone formation in prepubertal patients, encouraging a calcium-rich diet, and using vitamin D supplements.[25] Besides, chronically ill children should be advised to engage in weight-bearing physical activity since decreased physical activity is reported to negatively affect bone mass accrual.[26]

Considering the limited sample size in the current study and the flaws that may accompany studies of this kind, further long-term investigations are required to evaluate the precise relationship between osteoporosis in these patients and disease-related variables.

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original article

The prevalence and degree of resistance of *Plasmodium falciparum* to first-line antimalarial drugs: an in vitro study from a malaria endemic region in Yemen

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BACKGROUND: Unpublished studies on antimalarial drug efficacy have found low levels of chloroquine resistance in Yemen. This study was carried out to determine the current prevalence of drug resistance in *Plasmodium falciparum* in Yemen to the main anti-malarial drugs and to determine the effective concentration (EC) values.
METHODS: The WHO standard protocol was used for the selection of subjects, collection of blood samples, culture techniques, examination of post-culture blood slides and interpretation of results. The in vitro micro-test Mark III was used for assessing susceptibility of *P. falciparum* isolates.
RESULTS: The criteria for blood parasite density was met by 219 *P. falciparum* malaria patients. Chloroquine resistance was found in 47% of isolated *P. falciparum* schizonts. Mefloquine resistance was found in 5.2%. In addition, the EC50 and EC95 values in blood that inhibited schizont maturation in resistant isolates were higher than the normal therapeutic level for mefloquine. No resistance occurred against quinine or artemisinin, with no growth at the cut-off level for quinine and inhibition at low concentrations of artemisinin.
CONCLUSION: Our study confirmed the occurrence of chloroquine-resistant *P. falciparum* and a slow increase in the rate of this resistance; it is likely that resistance will increase further and spread over all the foci of malaria in Yemen. The low rate of mefloquine-resistant *P. falciparum*, was lower than that reported in Africa or Southeast Asia, but it is the first report of mefloquine resistance in Yemen. Finally, the isolates were sensitive to low concentrations of quinine and artemisinin.

Malaria is the most important parasitic disease of man. The human disease is a protozoan infection of red blood cells transmitted by the bite of the blood-feeding female anopheline mosquito. Approximately 270 million people suffer from malaria, and there are between one and 2.5 million deaths each year, mostly among African children.[1]

Antimalarial drugs fall into three broad groups: the quinoline-related compounds (quinine, quinidine, chloroquine, amodiaquine, halofantrine, primaquine), the antifols (pyrimethamine, proguanil, chlorproguanil, trimethoprim), and artemisinin compounds (artemisinin, artemether, artesunate). Of these, the artemisinin drugs have the broadest time window of action on the asexual malaria parasites, from the medium-sized rings to early schizonts, and produce the most rapid therapeutic responses.[2,3]

The problem of drug resistance is most important with *Plasmodium falciparum*. There is widespread but patchy resistance to proguanil and pyrimethamine wherever *Plasmodium falciparum* occurs. Chloroquine resistance has been known for years in parts of Southeast Asia, South America and Oceania. In the past decade, the prevalence and degree of chloroquine resistance have increased greatly in sub-Saharan Africa, at first in the east and later in the west of the continent.[4,5] In Yemen, several unpublished studies on antimalarial drug efficacy were carried out in the past two decades in the southern parts of the country by WHO consultants for malaria control. Their results showed a low level of chloroquine resistance, and although it appears to be not totally resistant, chloroquine remains a useful first-line therapy in Yemen.[6,7]

The main purpose of this study was to describe the state of drug-resistant malaria and to outline current thinking regarding strategies to limit the advent, spread and intensification of drug-resistant malaria in Yemen.

SUBJECTS AND METHODS

This study was conducted between August 2002 and March 2003. Patients of both sexes between the ages of 3.5 and 45 years living in Tihamah (Bajil city and surrounding villages) in the Republic of Yemen suffering from fever and/or other malaria symptoms were screened at field hospitals and malaria control centers. Rainfalls during 2002-2003 were recorded between May and October.

No selectivity parameters were taken except those required for the Mark III in vitro test technique.[8] Informed consent was obtained from patients or their parents. Fever was defined as a body temperature of 37.5°C or above. Patients were asked for any history of diarrhea and vomiting.

Any history of antimalarial drug ingestion within the past 2-4 weeks was an exclusion criteria. Only patients with negative urine tests to four aminoquinolines and sulphonamides were enrolled. Patients with complicated disease such as cerebral malaria, anemia, jaundice and bronchopneumonia were excluded. Enrolled patients were registered and given special codes. The diagnosis for all the patients was confirmed by the presence of asexual forms (trophozoite) of *P. falciparum* in the peripheral blood smear (thick film) and by the immunochromatography (HRP2) method as confirmation. Patients with mixed infections (*P. falciparum, P. malariae* or *P. ovale*) were excluded from the study.

Patients whose parasite count was not less than 1000 and not more than 80000 asexual parasites per mm^3 of blood were selected. The WHO in vitro antimalarial drugs susceptibility test (Mark III) technique[8] was used to determine the antimalarial drugs susceptibility of the *P. falciparum* isolates. The first choice drugs for malaria, which include chloroquine, quinine and artemisinin, were tested.

Data analysis was carried out using test-record sheets and the porbit analyzing program (WHO analyzing program) for interpretation of results.

RESULTS

During the 12 months of the study period, 219 Plasmodium falciparum malaria patients met our study criteria for parasite density in their blood. They comprised 156 males and 63 females; 183 passed the urine test for antimalarial drug absence (Table 1). For the 602 tests, the rate of successful schizont growth for the four drugs was 42% (Table 2). The frequency and percentage of *P. falciparum* schizont maturation for the different concentrations of the antimalarial drugs is shown in Table 3. The level of chloroquine resistance (cut-off indicating resistance) was calculated to be 8 pmol/well. At this cut-off, 47% of isolates showed resistance to chloroquine. The chloroquine values show the growth of five different schizonts at five different concentrations of chloroquine, which suggests the occurrence of

Table 1. Urine test results and patients selected for study.

	Tested	Positive urine test for anti-malarial drugs	Patients included in the study
Male	156	27	129
Female	63	9	54
Total	219	36	183

Table 2. Successful schizont maturation (positive culture), negative cultures and bacterial contamination.

Drug	Positive cultures	Negative cultures	Contaminated cultures	Total
Chloroquine	100	25	58	183
Mefloquine	58	36	71	165
Quinine	51	20	67	138
Artemisinin	47	12	57	116
Total	256	93	253	602

Number of cultures.

Table 3. The frequency and percentage of *P. falciparum* schizont maturation in the presence of different concentrations of the four antimalarial drugs.

Wells	Chloroquine*		Mefloquine**		Quinine***		Artemisinin****	
	n	%	n	%	n	%	n	%
B	4	4	3	5.2	6	11.8	3	6.4
C	9	9	25	43.1	15	29.4	13	27.7
D	40	40	19	32.8	17	33.3	17	36.2
E	31	31	8	13.8	10	19.6	8	17.0
F	9	9	3	5.2	1	2.0	6	12.8
G	5	5	0	0.0	2	3.9	0	0.0
H	2	2	0	0.0	0	0.0	0	0.0
Total	100	100	58	100.0	51	100.0	47	100.0

*The chloroquine dilution was from 1.0 to 64.0 pmol/per well; the cut-off value indicating resistance is 8.0 pmol per well (well E).

**The mefloquine dilution was from 2.0 to 128.0 pmol/per well; the cut-off value indicating resistance is 32 pmol per well. (Well F)

***The quinine dilution was from 4.0 to 256.0 pmol/per well; the cut-off value indicating resistance is 256 pmol per well. (Well H)

****The artemisinin dilution was from 0.15 to 150 pmol/per well, the cut-off value indicating resistance is not yet established.

Table 4. In vitro response of *Plasmodium falciparum* isolates to chloroquine, mefloquine, quinine and artemisinin.

Tested drugs	Sensitive		Resistant		Total
	n	%	n	%	
Chloroquine	53	53	47	47	100
Mefloquine	54	94.8	3	5.2	58
Quinine	51	100	0	0	51
Artemisinin	47	100	0	0	47

Table 5. Effective concentration (EC) in µmol/L blood for all isolates.and for sensitive (S) and resistant (R) isolates.

	EC50			EC90			EC95			EC99		
	S+R	S	R	S+R	S	R	S+R	S	R	S+R	S	R
Chloroquine	1.9	1.6	3.0	8.1	5.0	14.8	12.2	6.9	23.3	26.4	12.6	54.4
Mefloquine	1.5	1.5	0.6	6.3	6.2	13.7	9.4	9.2	33.1	20.2	19.4	71.8
Quinine	4.5	-	-	15.0	-	-	21.1	-	-	40.0	-	-
Artemisinin	0.1	-	-	0.9	-	-	1.6	-	-	5.1	-	-

five different strains of *P. falciparum* among our study patients. The cut-off for mefloquine was calculated to be 32 pmol/well with 5.2% of tested schizonts showing resistance to mefloquine. No resistance against quinine or artemisinin occurred in our study as indicated by no growth at the cut-off level (Table 3). Table 4 shows the schizont maturation rate for all drugs. Effective concentrations (EC) in blood for sensitive and resistant isolates are shown in Table 5. The EC50 and EC95 values for mefloquine that inhibited schizont maturation in resistant isolates were higher than the normal therapeutic level for mefloquine.

DISCUSSION

In our study, the first reason for selecting in vitro testing was that the alternative in vivo test used for the same purpose by WHO may be influenced by host factors such as malabsorption, immunity and other unpredictable factors, whereas our tool is not affected. In addition, the interpretations of the WHO in vivo test may be complicated in the case of resistance type I by re-infection during the 28-day follow-up period. The second reason is that in vitro testing can be done to test several types of drugs and drug combinations with different concentrations, while in vivo tests cannot. The third reason is that in vivo testing may lead to severe progression in a patient if the *P. falciparum* resists the tested drug, which may lead to complication and life-threatening infection, while with in vitro testing the patient can be treated with suitable drugs after collection of the specimen, and the failure of inhibition of *P. falciparum* in the well would not effect the patient's situation. In vitro testing was performed 183 times for chloroquine, 165 times for mefloquine, 138 times for quinine and 116 times for artemisinin. In total, 42.5% of in vitro testing of schizont maturation was successfully recorded, while 57.5% were affected by bacterial contamination or failure of schizont growth. Bacterial contamination occurs easily in field studies where the tests are carried out in remote areas without enough facilities to make the place of work sterile enough to prevent contamination of the culture wells. Cross-contamination during plate disposing and/or during harvesting procedures also can be a factor. In addition, the original contamination of the plates during preparation by the producer could not be excluded. Similar problems of high contamination have faced other researchers in malaria foci in Africa and Southeast Asia.[9]

The second problem was the failure of growing schizonts when there was no bacterial contamination. This might be due to the presence of antimalarial drugs in patient plasma in spite of negative results for the presence of antimalarial drugs in urine. Several recent reports confirm this suggestion and refer these phenomena to the long half-life of antimalarial drugs in plasma despite disappearance from urine. In addition, this failure may be related to technical errors (which are also quite common) such as pH change of the medium, direct contact of the BMM with ice during transfer and/or incubation interruption.[10]

Chloroquine

In Yemen, the occurrence of chloroquine-resistant *P. falciparum* strains were noticed in the early 1990s. In the last year, WHO and the National Malaria Control Program conducted an in vivo study to estimate chloroquine resistance in Tihamah, and their results showed that in more than 40% of the sample there was treatment failure in either early or late stages.[6,7] The WHO and our study confirmed the occurrence of chloroquine-resistant *P. falciparum* and indicated that the rate was rising slowly, but eventually was expected to increase and spread over all the foci of malaria in Yemen due to several reasons, the main reason being that chloroquine is one of the most widely consumed drugs in Yemen.[6,7] Others reasons are the high frequency of self-medication, inadequate dosing, and sub-therapeutic levels in the blood. These factors are believed to be predominant factors that contribute to chloroquine resistance in P. *falciparum*, not only in Yemen but also in most third world countries.[11,12]

One of the main aims of our study was to determinate the EC95. This result was needed to estimate the effective therapeutic drug level in the human body. Our results showed the EC95 for chloroquine was. 12.26 μmol/L of blood. This result indicates a high resistance of *P. falciparum* for chloroquine among the study cases, and this is confirmed by the EC95 which was equal to the 1.5 times (8 μmol/L blood) the therapeutic level required for treating cases of *P. falciparum* worldwide by chloroquine.[2,11,13]

Mefloquine

Mefloquine is a quinoline methanol compound available only for oral administration. It has a terminal elimination half-life of 2 to 3 weeks in patients with malaria.[14,15] *P. falciparum* mefloquine resistance has been reported from Southeast Asia and Africa.[16,17] In Yemen, no research has been done to study mefloquine resistance, so our study is the first in vitro test of mefloquine and the first to report the presence of mefloquine-resistant *P. falciparum* in Yemen. The resistance rate in our study was 5.6%. Our prevalence rate was lower than those reported from Africa (range from 20% to 65%) and from Southeast Asia (range, 30 to 80%).[18,19] Of the 11 isolates of mefloquine-resistant strains, 8 exhibited successful growth in 16 pmol/well (equivalent to 3.2×10^{-6} mol/L blood), which is the therapeutic level, and three isolates show a high degree of resistance growing in the 32 pmol/well (equivalent to 6.4×10^{-6} mol/L blood), which demonstrates that the mefloquine-resistant strains can adapt up to double the therapeutic level. In addition, the EC50 (1.4971 μmol/L blood) and EC95 (4.4971 μmol/L blood) confirmed resistance since these values are higher than the normal therapeutic level for mefloquine.[20]

Quinine

Reports of quinine resistance are still rare in Middle East countries, but a high rate of true resistance has been reported from Thailand (50%) and clinical failure of the quinine test has been reported from Africa.[21,22] In our study, no quinine resistance occurred and isolates of *P. falciparum* are still sensitive to quinine even at low concentrations of the drug, since the data show that the (SMI) schizont maturation index percentage of 97.6 occurred at 0.64 μmol/L blood. The high efficiency of quinine in Yemen is different from that reported in East Africa and other Middle East countries where there is a steady increase in the time parasites take to disappear from the blood after treatment with quinine.[21,22]

Artemisinin

The most important development in recent years has been the discovery and development of drugs related to artemisinin in China.[23] This drug is the best drug available for treatment of severe malaria in malaria drug-resistant *P. falciparum* areas. No resistance occurred in our study to artemisinin and the tested isolates were still very sensitive to low doses of the drug. Our result is similar to results reported from malaria foci worldwide where no artemisinin primary resistance was reported for the SMI (96%) of the isolates at 5.0 pmol/well and the EC95 was 1.64 pmol/well.

Our study confirmed both the occurrence of chloroquine-resistant *P. falciparum* and a slow increase in the rate of this resistance. It is likely that resistance will increase further and spread over all the foci of malaria in Yemen. It is recommended that the policy of treatment of malaria infection in the foci of chloroquine resistance be modified. The use of the combination of pyrimethamine/sulfadoxine as the first choice of treatment is recommended to avoid the spread of chloroquine-resistant *P. falciparum*. Investigation of the prevalence and degree of resistance of *P. falciparum* in malaria endemic foci in Yemen, and continual monitoring of the increasing resistance rate, is recommended as well. A molecular study to find out the drug-resistant *P. falciparum* strains in Yemen, which this study suggests to be five in number, is also needed. A low rate of mefloquine resistance in *P. falciparum* is present in Yemen, and it is lower than rates reported from Africa and Southeast Asia. To prevent the further development of mefloquine-resistance in Yemen, the drug should never be used in isolation and a combination with sulfadoxine and pyrimethamine should be used. Finally, no quinine or artemisinin resistance occurred and isolates of *P. falciparum* are still sensitive to quinine and artemisinin even at low concentrations of both drugs. The SMI percentage, EC90, and EC95 of both drugs should be evaluated from time to time and correlated with previous results. This will provide good information about the situation of these drugs in Yemen as well as for other drugs and combinations.

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original article

Clinicopathologic features of hepatic neoplasms in explanted livers: a single institution experience

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BACKGROUND: Hepatic neoplasms can be the primary indication for hepatic transplantation. The tumors can also be incidentally identified in explanted livers. We explored the clinicopathologic features of hepatic neoplasms identified in explanted livers.

MATERIALS AND METHODS: All explanted livers resected between 2001 and 2006 were evaluated for the presence of neoplasms and their clinicopathologic features were examined.

RESULTS: In 98 liver transplants, 15 neoplasms (15.3%) were identified. Patient ages ranged from 5 to 63 years (median, 56 years). The primary etiology of hepatic disease was hepatitis C virus in 12 cases, hepatitis B virus in 1 case, cryptogenic cirrhosis in 1 case and congenital hepatic fibrosis in 1 case. Serum alpha-fetoprotein was significantly elevated (>400 U/L) in only 2 cases. CA19-9 was not elevated in any of the cases. The tumors included hepatocellular carcinoma (HCC) in 13 cases, 1 case of cholangiocarcinoma and 1 case of combined HCC and hepatoblastoma. The tumors ranged in size from 0.5 to 5 cm (median 1.4 cm) and were multifocal in 5 of the cases (33%). Tissue alpha-fetoprotein expression was only seen in the cases associated with elevated serum levels.

CONCLUSION: In our institution hepatic neoplasms are seen in more than 15% of explanted livers. They can be incidentally identified, are frequently not associated with elevated serum levels of alpha-fetoprotein and CA19-9, are commonly multifocal but small, and are associated with good prognosis. Elevated serum alpha-fetoprotein, albeit specific, is not a very sensitive marker in the detection of hepatic neoplasms.

The presence of a hepatic neoplasm is one of the indications for hepatic transplantation. Currently less than 10% of hepatic transplantation is performed for hepatic malignancy.[1] Patients with hepatic neoplasms fulfilling the Milan criteria are good candidates for hepatic transplantation.[2] Hepatic neoplasms can be incidentally identified in explanted livers without the pre-operative suspicion of the presence of a neoplasm.[3,4,5] One other indication for hepatic transplantation is markedly increased levels of serum alpha-fetoprotein in patients with end-stage hepatic disease waiting for transplantation.[6] The prognosis of hepatic transplantation for hepatic neoplasms depends, in large part, on certain clinicopathologic parameters. These include tumor size, grade, vascular invasion and the general clinical condition of the patient.[7,8,9] In this study we attempted to analyze clinicopathologic parameters of hepatic neoplasms identified in explanted livers in our institution to see if we could identify features that would help us more properly manage patients with end-stage liver disease preparing for transplantation.

MATERIALS AND METHODS

All explanted livers resected for hepatic transplantation at King Faisal Specialist Hospital and Research Center between the years 2001 and 2006 were reviewed. Cases with the diagnosis of a hepatic neoplasm were selected. The slides and reports pertaining to the resected liver were reviewed. The tumors were histologically evaluated by three pathologists (WAM, MAO and HA). The tumor size was obtained from the gross pathology report and the tumors were classified and graded

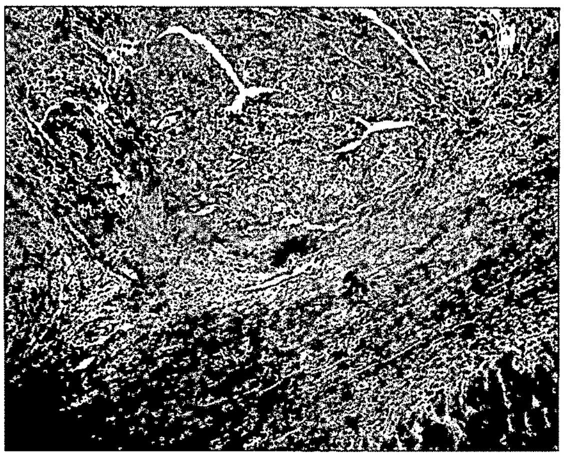

Figure 1a. Case of grade 1 hepatocellular carcinoma (top) with a thick capsule and adjacent reactive hepatic tissue (bottom). Serum alpha-fetoprotein was slightly increased and tissue alphafetoprotein was negative (H&E stain X100).

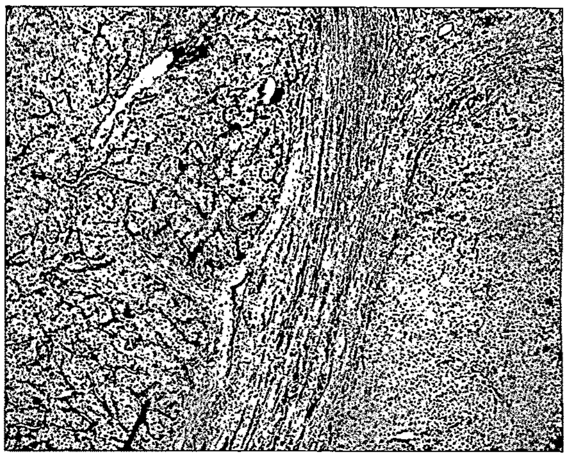

Figure 1b. Same case as Figure 1a of grade 1 hepatocellular carcinoma showing CD34 expression in the tumor nodule (left) with lack of expression in the reactive liver (right) (immunoperoxidase X50).

according to the Edmondson grading system for hepatocellular carcinoma.[10] Immunohistochemical stains for alpha-fetoprotein and CA19-9 were performed in all cases. CD34 immunostaining was performed for low-grade neoplasm to highlight the vascular pattern of the neoplasms. Patient charts were reviewed. The clinical data pertaining to age, sex and primary hepatic disease were tabulated. Laboratory findings related to serum levels of alpha-fetoprotein and serum CA19-9 pre- and post-transplantation were also obtained from patient charts. Clinical status related to patient condition in relation to survival, recurrence of tumor and serum levels of alpha-fetoprotein and CA19-9 at last follow up were also recorded.

RESULTS

There were 98 hepatic transplantations performed in our institution between the years 2001 and 2006 and 15 neoplasms, representing 15.3% of all transplants, were identified. Patient ages ranged from 5 to 63 years (median, 56 years). There was only one child among the group of transplanted patients that had a hepatic neoplasm. The primary underlying indication for transplantation was hepatitis C in 12 cases (80%), hepatitis B in one case, cryptogenic hepatitis in one case and congenital hepatic fibrosis in one case.

Serum alpha-fetoprotein was significantly elevated (>400 U/L) in only two patients (6.6%). One patient had serum alpha-fetoprotein of 10 000 U/L and the other had a level of 700 U/L. None of the patients had an elevated level of serum CA19-9.

Clinical and radiologic suspicion of the presence of neoplasm was present in 13 of the patients. Two patients had no preoperative clinical suspicion for the presence of neoplasm.

Of the 15 tumors identified, hepatocellular carcinoma was seen in 13 cases (86.6%). There was one case of cholangiocarcinoma and one case of combined hepatocellular carcinoma and hepatoblastoma. The tumor grade was Edmonson grade 1 in two cases, grade 2 in 11 cases and grade 3 in one case. The two low-grade tumors required the use of CD34 immunostain to highlight the vascular pattern of the neoplastic nodule in comparison to the diseased liver (Figure 1a, b). Only two cases showed expression of alpha-fetoprotein in the neoplasm including a case of hepatoblastoma and high-grade hepatocellular carcinoma (Figure 2a, b). This corresponded to the two cases showing elevated serum levels.

The 15 tumors ranged in size from 0.5 cm to 5.0 cm in greatest diameter with a median diameter of 1.4 cm. The tumors were multifocal and microscopic in five of the cases (33%). Four tumors (26.6%) were missed on initial pathologic examination and identified upon pathological re-examination of the explanted liver at the request of the transplantation surgeon.

The only pediatric patient in our series was an 8-year-old female with a history of congenital hepatic fibrosis. She presented with markedly elevated serum alpha-fetoprotein (10 000 U/L). No evidence of a neoplasm was clinically or radiologically suspected. After the liver was explanted a critical review of the CT scan of the liver showed focal hypodense hepatic lesions in segment #7 (Figure 3). She received a living-related liver transplantation. Examination of the liver showed end-stage hepatic cirrhosis with multiple microscopic foci of hepatocellular carcinoma and hepatoblastoma (Figure 4a, b). Several weeks post-operatively the serum levels of alphafetoprotein returned to normal. The patient was free of disease one year after transplantation.

Follow-up information ranging from 4 to 48 months was available on all patients with a median follow up period of 20 months. Two patients died of primary graft failure and all other patients are alive with no evidence of recurrence or residual disease.

DISCUSSION

Hepatocellular carcinoma shows tissue expression of alpha-fetoprotein in 20% to 40% of cases.[10] Tissue expression in our series was seen in only 13.3% of the cases. It has been shown that tissue expression of alpha-fetoprotein corresponds to high serum levels and high-grade tumors.[11] This finding was confirmed in our series where tissue expression corresponded to serum levels of alpha-fetoprotein. The only two cases that showed tissue expression of alphafetoprotein had elevated serum levels. The cases were high-grade hepatocellular carcinoma and hepatoblastoma. This finding suggests that most hepatocellular carcinomas do not express alpha-fetoprotein either at the tissue level or at the secretory level. This indicates the low sensitivity of the test and suggests the need for a more sensitive test for early detection of hepatocellular carcinoma.

The rate of incidentally identified neoplasm in explanted livers ranges from 10% to 50% of the cases depending on the study.[3,12] This rate depends on how closely patients with end-stage hepatic disease are followed. The rate is low in developing countries and higher in developed ones. We found incidental neoplasms in 13% of our series. Four cases required repeated gross inspection of the explanted liver to identify the neoplasm upon request of the transplant surgeon. This was mainly due to the small size of the tumors. The tumors were also well differentiated in many incidents requiring the use of immunohistochemistry to differentiate the nodules from the cirrhotic reparative nodules. It therefore appears that it is extremely important to thoroughly examine explanted livers to identify small multifocal neoplasms.

Tumor size and grade are two of the most significant prognostic indicators in hepatocellular carcinoma. In one study, large tumor size and high tumor grade could predict vascular invasion and a poor outcome.[13] Another study showed that tumor size together with Ki-67 proliferation index and p53 expression are the most significant prognostic indicators. None of our patients succumbed to their diseases. This may be mainly explained by the predominantly small size of the primary tumors

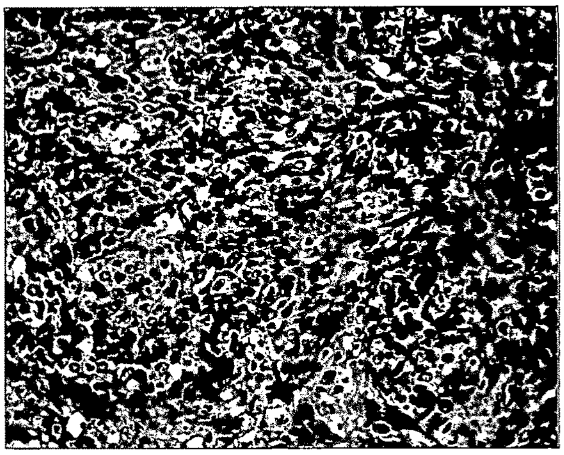

Figure 2a. Case of grade 3 hepatocellular carcinoma with focal sarcomatoid changes (H & E X400).

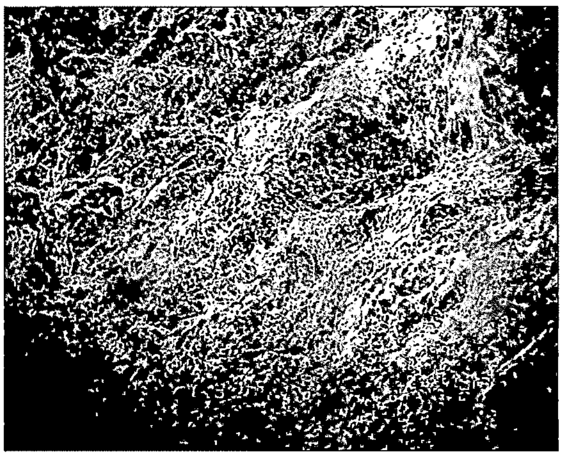

Figure 2b. Same case as Figure 2a showing strong expression of alpha-fetoprotein. Serum alpha-fetoprotein was 700 U/L (Immunoperoxidase X200).

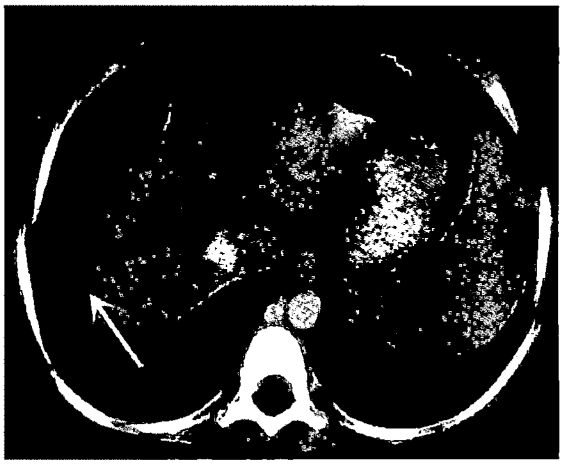

Figure 3. Transverse contrast enhanced CT demonstrated focal hypodense hepatic lesion in segment # 7 with focal central enhancement (nodule-in-nodule) represents hepatocellular carcinoma within a dysplastic nodule (arrow).

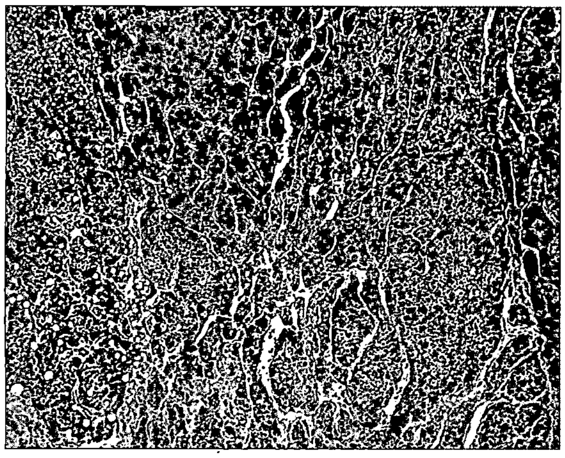

Figure 4a. Case of combined hepatocellular carcinoma (top) and hepatoblastoma (bottom) in an 8-year-old female (H&E X200).

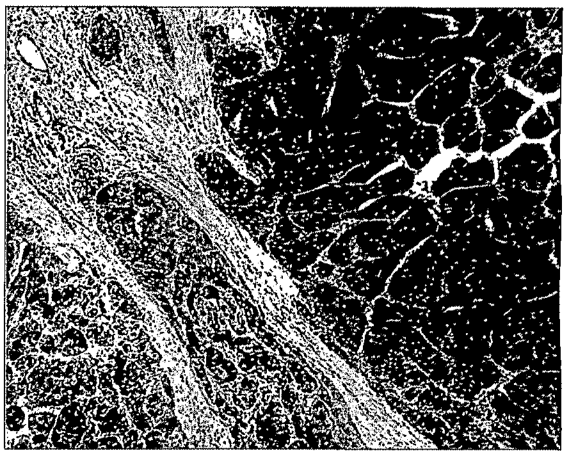

Figure 4b. Case of combined hepatocellular carcinoma and hepatoblastoma showing strong expression of alpha-fetoprotein. The patient serum level of alpha-fetoprotein was 10000 U/L (Immunoperoxidase X200).

and the prevalence of low grade. Malignant neoplasms are one of the indications for hepatic transplantation.[1] Patients with chronic end-stage hepatic disease who develop clinical or radiographic evidence of a neoplasm are candidates for hepatic transplantation, especially if the tumor is resectable with no evidence of metastasis. This is especially true when the tumor is associated with marked elevation of serum alpha-fetoprotein.

Serum levels of alpha-fetoprotein have been shown to be markedly elevated in more than 60% of cases of hepatocellular carcinoma.[6,10] Levels above 400 U/L have been suggested as a surrogate test for the presence of a neoplasm.[16] Although high levels have been seen in non-neoplastic conditions of the liver such as hepatitis C, this occurrence is not very frequent.[15] These levels would, however, rarely reach levels associated with neoplasms (>400 U/L). In our series, we did not see a high incidence of elevated serum alphafetoprotein. Less than 20% of our cases were associated with markedly elevated levels of serum alpha-fetoprotein. Extremely high levels of serum alpha- fetoprotein have been linked with poor prognostic indicators such as large tumors, vascular invasion and poor survival.[16] Our patients had smaller tumors and better survival.

Paradoxically, one of our patients had extremely high levels of alpha-fetoprotein without any clinical or radiographic evidence of a neoplasm. The resected liver showed multiple microscopic foci of hepatocellular carcinoma and hepatoblastoma. This may indicate that extremely high levels of alpha-fetoprotein may be seen in the absence of clinically or radiologically detectable tumor. This also suggests the level of serum expression of alpha feto-protein may be related to individual cell expression of the protein usually seen in high grade neoplasms and hepatoblastoma rather than being related to tumor size or vascular invasion. It thus seems that markedly elevated levels of serum-alpha-fetoprotein in patients with long-standing chronic liver disease with failure may be suggestive of a hepatic neoplasm and an indication for hepatic transplantation even in the absence of a clinically or radiologically detectable tumor.

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brief report

Symptomatic congenital heart disease in the Saudi Children and Adolescents Project

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The word 'prevalence' of congenital heart disease (CHD) usually means the estimated population of people with CHD at any given time. The term 'incidence' of CHD means the annual diagnosis rate or the number of new cases of CHD diagnosed each year. Most of the recent studies in the Gulf region measured the incidence of CHD in children.[1,2] There are various local studies on the pattern of CHD,[3,4] and these studies are descriptive analyses of a selected sample. Our study is the first community-based national prevalence study of symptomatic CHD in children and adolescents in Saudi Arabia, and includes CHD presenting with symptoms or clinical signs. Excluded are asymptomatic patent ductus arteriosus in the first 3 months of life; simple bicuspid aortic valves; isolated peripheral pulmonary artery stenosis with no clinical significance; and minor atrial shunts across defects measuring less than 5 mm.

METHODS

Our study was part of the Health Profile of the Saudi Children and Adolescents Project. The sample was 45 682 children and adolescents of ages from birth to 19 years selected by multistage probability random sampling of Saudi households from a stratified listing based on the population census of the 13 regions of the country including major cities, small towns and villages. A house-to-house visit by the field team, which included a physician, was made to all the households in the sample. A questionnaire that included age, gender, medical history and physical examination was completed. The results of the interview and clinical examination allowed classification of the children into one of the following categories:

a) Children with a known diagnosis of CHD, confirmed with medical reports and echocardiography results from the concerned hospitals. These children were classified according to diagnosis into 4 groups (Table 1).

b) Children with a known diagnosis of CHD but without supporting medical reports from concerned hospitals. The diagnosis was based on what the families were told about echocardiography results by treating doctors. These children were labeled as unspecified congenital heart disease (Table 1).

c) Children with a history and clinical signs suggesting cardiac disease that were not diagnosed before, who were referred to hospitals. The hospital diagnosis was based on clinical examination and echocardiography. These children were included in the study after the diagnosis was provided by local hospitals and classified as category (A) into 4 groups.

Table 1. Prevalence of congenital heart diseases in Saudi children.

Diseases	Number of cases			Prevalence per 10 000
	Males	Females	Total (%)	
Ventricular septal defect	18	26	44 (46)	10
Atrial septal defect	2	6	8 (8.5)	2
Other non-cyanotic CHD*	3	4	7 (7.5)	2
Cyanotic CHD†	5	5	10 (11)	2
Unspecified CHD	14	12	26 (27)	6
Total CHD	42	53	95 (100)	21

*Patent ductus arteriosus 1, coarctation of the aorta 1, aortic stenosis 2, pulmonary stenosis 2 and Ebstein's anomaly 1. †Tetralogy of Fallot 3, transposition of great arteries 2, complex cyanotic heart disease 5.

RESULTS

During the period 2004-2005, of a total of 45 682 children and adolescents, 95 had CHD for a prevalence of 21 per 10 000. The types of diseases are shown in Table 1. Ventricular septal defect (VSD) was the commonest diagnosis, occurring in 44 of the 95 (46.3%) children with CHD with the highest prevalence of 10 per 10 000.

Table 2. Prevalence of congenital heart disease in children and adolescents worldwide.

Study description	Prevalence per 10 000 population	Children Number	Year	Age	Place Of Study
Community-based study	21	45 682	2005	Birth - 18 yrs	Saudi Arabia (present study)
Population-based study	37	4390	1993	0-1year	USA: Baltimore-Washington Infant Study[7]
Population-based study	47	330 017	2003	Live and still births	Italy: Emilia-Romagna Registry, Calzolari E[6]
Population-based study	61	815 569	1999	0-15 years	Czech Republic: Bohemia Survival Study, Samanek M[5]
School-based study	10	1788	2000	5-15 years	Egypt: Alexandria, Zaki[9]
School-based study	20	13 322	1997	5-15 years	Sudan: Sahafa Town, Khalil[10]
School-based study	13	9420	2003	5-18 years	Nepal: Kathmandu, Bahadur[8]
Community-based study	42	11 833	2001	0-15 years	India: New Delhi, Chadha SL[18]
Community-based study	50	48 638	2005	3-18 years	China: Yunnan Province, Jiang[19]

The next most common group was unspecified CHD in 26 of 95 (27.4%) for a prevalence of 6 per 10 000. The remainder of the cases, such as cyanotic CHD, atrial septal defects (ASD), and other non-cyanotic CHD occurred much less commonly with a prevalence of about 2 per 10 000 each.

The distribution of CHD according to sex of patients showed a slight predominance in females, with 53 girls and 42 boys, for a female to male ratio of 1.3:1 (Table 1). VSD was slightly more common in females with a female to male ratio of 1.4:1. ASD was seen more in girls with a female to male ratio of 3:1. Cyanotic CHD was equal in both sexes.

The regional distribution of CHD showed that the Central Region had the highest prevalence of 27 per 10 000, followed by the Northern and the Eastern Regions, with a prevalence of 25 per 10 000 each and the Southwestern Region prevalence of 21 per 10 000. The prevalence was less common in the northwestern region, with 10 children only (prevalence 9 per 10 000). To assess the prevalence of CHD more accurately, the results were related to sample size in each region: North Western Region (Makkah and Madinah regions)=10 711, Central Region (Riyadh and Qassim regions)=11 194, Eastern Region (Damam region)=4420, Northern Region (Jouf, Northern Border, Hail and Tabuk regions)=8 959, and the Southwestern Region (Assir, Gizan, Najran and Al Baha regions)=10 398.

DISCUSSION

The prevalence of CHD in Saudi children is compared with other studies in Table 2. The prevalence in our study was lower than in hospital-based studies due to variations in methods and age differences,[5-7] whereas the prevalence was higher than in school-based studies due to age differences.[8-10] The prevalence of CHD is related to the relative frequency of VSD,[11] the most common type of CHD.[12-13] The majority of VSD are closed spontaneously in early childhood,[8,9,14] so the prevalence of CHD in this community-based study (which includes a wide age range) was expected to be lower than in hospital-based studies, which are done usually in infants or newborns.[5-7,13] The prevalence of CHD also depends on the diagnosis of minor cardiac defects such as small atrial septal defect, small patent ductus arteriosus, and mild pulmonary valve stenosis.[11,15-17] These minor lesions were not diagnosed in this community study due to subtle clinical signs. Most newborns with severe types of complex cardiac lesions die before 1 year of age, which also reduces the prevalence of CHD in older children.[5,7,9,14] These factors explain the low prevalence of CHD in this study in comparison with hospital-based studies.[6,7]

Our study showed a low prevalence of CHD compared with similar community-based studies in other countries such as China and India, which is either due to actual low prevalence in Saudi Arabia or under-reporting of cases during the survey (Table 2). The prevalence was 42 per 10 000 in Indian children younger than 15 years[18] and 50 per 10 000 in Chinese children (aged 3-18 year),[19] which are higher than the prevalence of 21 per 10000 in Saudi Arabia.

According to the KFSH study,[20] the southwestern egion of Saudi Arabia near the border with Yemen and the northern part of the Eastern Region appear to exhibit a higher burden of CHD. Our study demonstrates a Central Region dominance followed by the Eastern Region and the Northern Region, with the last being the Southwestern Region. The KFSH study was hospital-based using data on admitted patients, while our study was community based, which explains the difference between the two studies.

A limitation of our study is that the group of children with unspecified CHD is a large group (27% of total children with CHD). These children were diagnosed as having CHD, but without supporting medical reports from concerned hospitals and thus our diagnosis is based on history and clinical examination only. These children were kept in a separate group to avoid bias and included in the total prevalence of CHD in the Kingdom, but their significance in the prevalence of various types of CHD cannot be ignored.

This nationwide community-based study for CHD has revealed a relatively low frequency of CHD, the commonest being VSD, with the frequency lower than reported from other populations. We still need supportive community-based studies to measure the prevalence of CHD in different regions of the country. In addition, we need a multicentric study on the epidemiology of CHD to assess the pattern of CHD in Saudi Arabia, and the survival and outcome of affected babies.

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brief report

Cochlear implantation in Bahrain: promising results

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Cochlear implantation (CI) has been established worldwide as an effective method of rehabilitation of the profoundly hearing impaired patient at any age.[1,2] CI provides the possibility for the deaf to hear up to normal levels, for adults who had postlingual deafness to regain their speech, and for prelingually deaf children to develop speech and language if implanted at a suitable age and provided with appropriate rehabilitation. The CI program started in the Kingdom of Bahrain in 2001, at Salmanyia Medical Complex (SMC), and was supported by the Ministry of Health. The CI surgeries on the program stopped in years 2003 and 2004 due to financial reasons, and restarted in 2005. This study was designed to evaluate the result in relation to hearing gain and speech development after rehabilitation of CI surgeries performed in Bahrain in the years 2001 and 2002.

PATIENTS AND METHODS

All CI surgeries performed in SMC in 2001 and 2002, were included in this study. Cases referred for CI were evaluated at the Hearing Impaired Children Clinic (HICC) by a team including an ENT consultant CI surgeon, an audiological physician, speech therapists and a pediatric developmental physician. Children had an otolaryngological and audiological assessment, a CT scan of the temporal bone and an MRI of the inner ear and brain. Psychiatric evaluation was requested when needed.

Selection criteria to implant children were (1) prelingual deafness aged ≤5 years of >90 dB hearing loss of average 0.5,1,2 and 4 KHz without speech development, and no benefit from hearing aid, or (2) prelingual deafness aged 6 to 15 years with residual hearing of 90 dB, but with residual speech and limited benefit from hearing aid, or (3) postlingual deafness aged up to 15 years with a hearing level of ≥90 dB, after acquiring speech. The surgeries were performed from May 2001 to October 2002.The CI device used was a Med El, Combi 40+.

Programming was performed 6 weeks after surgery. Rehabilitation was provided for periods of one to two years, on individual and in nursery setting sessions at Prince Sultan Bin Abdul Aziz Hearing and Speech Development Center of the Bahraini Child Development Society. The patients were called to the clinic (HICC) in November and December 2005 for a post-CI hearing and speech evaluation. According to the age of the child, hearing was evaluated by free-field or pure tone audiometry in the frequencies 0.5, 1, 2, and 4 KHz. Speech and language perception and production were tested by monosyllabic and bisyllabic word list based on the Ashoor Arabic speech audiometry list [3,4] and by a closed set list of 10 sentences in Arabic created at our center. Words or sentences were presented by the testing person standing at 1-meter distance behind the child. This is similar to the method described by Vaewvichit et al.[5]

RESULTS

CI surgeries were performed on 15 children, including 10 females (67%), and 5 males (33%). Thirteen (87%) had prelingual deafness, including 9 (60%) of age 5 years or less (mean age, 3.6 yrs) and 4 (27 %) of 11-15 years (mean age, 14.7 years). The remaining 2 cases (13%), one male and one female, had postlingual deafness and were aged between 6-10 years (mean age, 9.5 years). The overall mean age for the 15 cases was 7.0 years.

Hearing level before implantation according to testing by free field, pure tone audiometry, and acoustic brain reflexes (ABR) showed no responses in 11 cases (73%), and a hearing level of 90-100 dB in 4 cases (27%). The etiological factors were hereditary in 6 cases (40%), all having consanguinity of the parents and a family history of deafness. The causes were anoxia at birth in 2 cases (13 %), meningitis in 1 case (7%) and renal failure in 1 case (7%). The remaining 5 cases (33%) were of unknown etiology. Postimplantation and after acquiring auditory skills of sound detection, all children had hearing responses at levels from 20 dB to 45 dB.

Table 1. Fifteen patients by age, sex and post-implantation hearing and speech results.

Age at Surgery (years)	Sex	Hearing Loss (dB)		Recognition (%)	
		Preoperative	Postoperative	Words	Sentences
15	F	90-100	20- 30	100	100
9	M	NR	30- 40	100	100
5	F	NR	20 – 30	100	90
14	F	90-100	20-40	100	100
3	F	90-NR	25-30	100	100
11	F	100-110	25-30	100	100
4	F	NR	25-30	100	100
6	M	NR	30-45	0	0
15	F	90-110	30-40	100	100
14	F	90-100	20-40	50	40
2	M	90-100	20-40	100	100
1	M	NR	20-40	100	100
2	F	NR	35-45	50	40
3	M	NR	30-45	0	0
2	F	90-100	20-40	70	50

NR = No response to hearing tests. Cases listed according to time sequence of CI surgery.

The poorer responses were in the two children who had poor speech development as indicated below.

Thirteen children (87%) had satisfactory to excellent responses on the words and sentences closed set lists. Ten (77%) had excellent responses of 90% to 100%, and 3 (23%) had satisfactory responses between 40% to 70%. All have joined normal nursery or school (Table 1). The remaining 2 cases (13%) failed to respond to acceptable levels without lip reading. These 2 cases were considered failures in speech development. They were re-evaluated and diagnosed as having poor cognitive function.

There were no major surgical complications. In one patient who had thick skin over the receiver, the wound was reopened and the skin was thinned 3 months after surgery. Two patients (13%) had technical failure of the internal device. One had the failure in 2002, one year postimplantation. The other child, who was implanted in 2001, at age 15 years, had failure of the device after 5 years of implantation, in March 2006. In both cases the device was replaced with a new internal device from the same firm.

DISCUSSION

The etiological factors in the implanted deaf children in this study are comparable to other studies on deafness and implantation, such as our study on the etiology of sensorineural hearing loss in children in Bahrain,[6] and other studies[7,8] indicating that the major factor is genetics, presenting as congenital hereditary deafness in 40% and deafness of unknown etiology in 33%. Both factors are related to the high rate of consanguineous marriage. Our selection criteria for CI in deaf patients were comparable to other studies and to standards of selection of patients in traditional textbooks.[9]

As indicated by Gysin et al,[7] complications of CI include major complications (4%), minor complications (3%) and device failure (2%). Operative and postoperative complications range from cerebral infarct or cardiac infarct and death, meningitis, facial nerve injury, chorda tympani injury, and tympanic membrane injury to iatrogenic cholesteatoma, inappropriate electrode insertion, wound infection and other complications, for an overall rate of 11.8%.[1,2] In our study, complications were rare except for device failure in two cases for a failure rate of 13.3%. The high percentage of device failure in our study is due to the small number of cases.

Sound detection and awareness, along with word recognition of different test lists, has been shown to vary among implanted patients with various factors associated with the outcome. Duration of deafness and to a lesser extent, age at implantation, are the most significant predicators of outcome. The shorter the duration of deafness, the better is speech understanding with the implant. Most recent studies emphasize the importance of implantation at an early age for better performance.[10] In most studies, no clear relationship has been found between etiology and postoperative performance, while patients with meningitis were more frequently in the poorer performing groups of implant users.[11]

Postimplantation results show variable levels of speech perception, including a poor response for the House 3M device and responses from chance (4%) up to excellent (92%) in nucleus device patients.[5] Lenarz et al[12] stated that "on average, auditory performance improved over time up to 18 months after implantation, closed set test increased by 25% to 55% in 18 months, open set score began to show improvement between 6 and 12 months postoperatively" in 18 children using a Clarion 1.2 device. On the other hand, Kiefer et al[13] indicated that all children had a clear benefit from implantation, and that 10 of 21 prelingually deaf or hearing impaired children had reached some degree of open set speech understanding only 15 months postoperatively. In their study they used Med El Combi 40/Combi 40+.

We conclude that the 15 children implanted in 2001 and 2002 as first group of children on the CI program in Bahrain had overall improvement in 13 (87%) in relation to hearing gain and speech perception and development of satisfactory to excellent levels. These children were able to integrate into the normal schools and nurseries. The remaining 2 cases (13%) failed to respond to acceptable levels without lip reading, a failure related to poor cognitive function.

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case report

Severe neonatal pulmonary hypertension secondary to antenatal maternal diclofenac ingestion reversed by inhaled nitric oxide and oral sildenafil

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The nonsteroidal anti-inflammatory drugs (NSAID), which act as inhibitors of prostaglandin synthesis, are widely used in clinical practice as tocolytic agents.[1] Administration of these agents in pregnancy, however, carries a potential risk to the fetus. Indomethacin can cause premature closure of the ductus arteriosus,[1] which may lead to serious fetal and neonatal complications including oligohydramnios, hyperbilirubinemia, pulmonary hypertension, necrotizing enterocolitis and intraventricular hemorrhage.[2,3] Diclofenac (*Voltaren*), closely related to indomethacin, is one of the group used to treat pain and fever, and it may cause the same fetal and neonatal complications.

CASE

A 37-year-old Saudi woman had an uneventful pregnancy until 38 weeks gestation when she was operated on for thrombosed hemorrhoids. She was given diclofenac sodium for pain, 50 mg orally three times a day. After 3 days she noticed decreased fetal movement. Subsequently, oligohydramnios and fetal distress developed, which led to cesarean section. The baby weighed 2900g. Soon after birth the baby developed severe respiratory distress and cyanosis. After a trial of aggressive ventilation for severe hypoxemia at the referring hospital, she showed no improvement. Oxygen saturation was 60% on FiO2 of 100% and her oxygen index (OI) was 40. She was resuscitated and transferred to our institution at 20 hours of age. An echocardiogram done at the referral hospital and repeated in our center revealed right ventricular hypertrophy, moderate tricuspid regurgitation, closed ductus arteriosus and severe pulmonary hypertension. A high frequency oscillatory ventilator (HFOV), dopamine, dobutamine and milrinone all failed to improve oxygen saturation. Inhaled nitric oxide (iNO) at 20 ppm also resulted in no improvement. After 2 days, sildenafil was added as adjunctive therapy at 0.15 mg orally every eight hours. Within 24 hours oxygen saturation improved to 88% and the OI declined to 15 (Figure 1). iNO was weaned and then completely discontinued. Sildenafil was given for 2 weeks. The baby was discharged in excellent condition at 3 weeks of age. Two weeks later, the echocardiogram was normal.

DISCUSSION

The pathophysiology leading to pulmonary hypertension in our patient is most likely related to NSAID exposure in late gestation. The patency of the ductus arteriosus is maintained in utero with dilatatory prostaglandins such as (prostaglandin E). Closure of the fetal ductus arteriosus in utero can be either spontaneous or due to pharmacological agents such as NSAIDs.[4] It usually begins with progressive constriction of the vessel walls, which initially leads to very high flow velocities from the pulmonary trunk towards the descending aorta.[5] In cases with severe constriction or closure, the ductus arteriosus can no longer function as a conduit of right ventricular flow into the descending aorta. More blood is directed to the pulmonary arteries, which leads to pulmonary hypertension.[1] Although most studies involved indomethacin in animal models, Mommas et al,[6] who studied the effect of various NSAIDs on the ductus of fetal rats, demonstrated that diclofenac exerts an equally severe constrictive action as indomethacin. Thus, fetal exposure in late gestation provides the likely explanation for increased susceptibility to irreversible ductal constriction followed by severe pulmonary hypertension in our patient. Zenker et al reported a similar case where he used iNO alone. It required 22 days

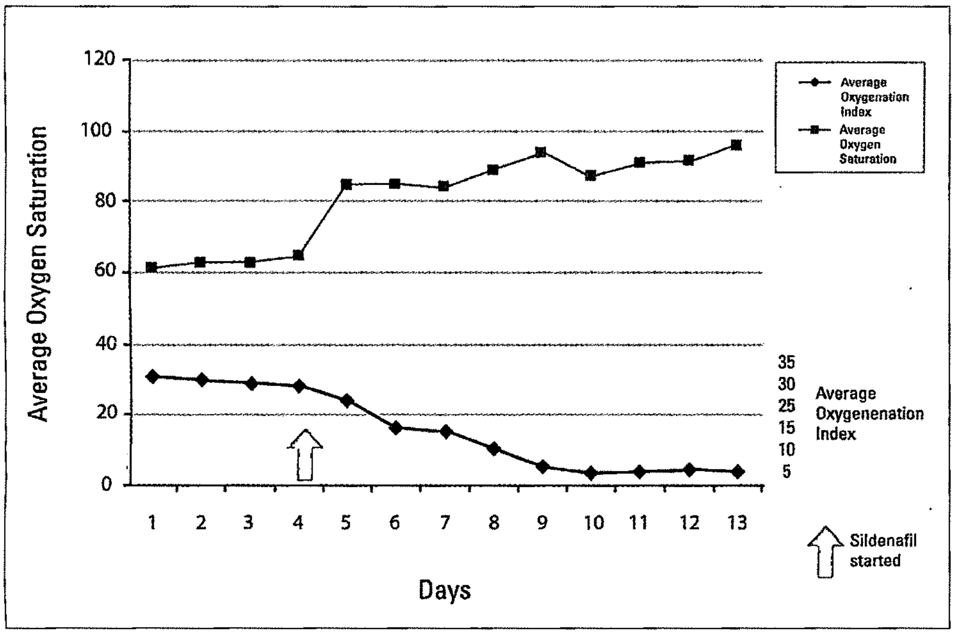

Figure 1. Average oxygen index and oxygen saturation in the neonate over first 2 weeks of life.

for pulmonary hypertension to be controlled and the patient subsequently developed papillary muscle necrosis.[6] Our patient was perfectly healthy at discharge and at follow up in 4 weeks.

Our experience replicates those reported by Kendavello et al and Atz et al, where sildenafil had an augmentation effect and prevented a rebound pulmonary hypertension or hypertensive crisis during weaning of nitric oxide. The addition of sildenafil lead to a shorter duration of therapy and minimized the possible damaging effects of pulmonary hypertension and its complications.[7,8]

When pulmonary hypertension occurs, early transfer to a tertiary care center with the availability of nitric oxide should take place as soon as possible. In severe cases with pulmonary hypertension with suboptimal response to iNO, adjunctive therapy with sildenafil should be considered. Our experience and that of others[8,9] should be confirmed by randomized double blind controlled studies to prove the safety and efficacy of sildenafil in neonates. Pregnant women should be instructed not to use NSAIDs during pregnancy.

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case report

Barium meal followthrough and CT findings in paraduodenal hernia

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An internal hernia is defined as the protrusion of the viscus through a normal or abnormal opening within the confines of the abdominal cavity. It constitutes 0.2% to 0.9% of all cases of intestinal obstruction.[1] Internal hernias are either congenital or acquired. Acquired hernias usually result from failure to close the mesenteric defect after bowel resection. Congenital hernias are paraduodenal (53%), transmesenteric (12%), at the foramen of Winslow (80%), paracecal (6%) and transomental (<5%).[2]

Because of the risk of strangulation of the hernia contents, even small hernias are dangerous and may be fatal.[3,4] They may also present with vague chronic intermittent abdominal pain.[1] Clinical and radiological diagnosis in the asymptomatic stage is probably impossible. With time and repeated episodes of herniation, the mesenteric defects enlarge and long segments of small bowel may herniate more, twist and become obstructed and ischemic.[1]

Paraduodenal hernia is the commonest type of internal hernia[3] and accounts for more than 50% of internal hernias.[3,5] It is left sided in 75% of patients[3,6] and is believed to occur because of congenital herniation of the small bowel into the left paraduodenal fossa of Landzert,[6] which is a peritoneal pocket present in 2% of autopsies.[5]

Hernias are rarely diagnosed preoperatively.[3,4] Several suggestive findings on upper gastrointestinal series include an abnormal position of the third portion of the duodenum, the presence of an ovoid intestinal mass, delayed transit of contrast through the small bowel, and an absence of small bowel in the pelvis.[7] In recent years, computed tomography (CT) has begun to play an important role in the diagnostic workup of suspected paraduodenal hernia.[8]

In this report, we describe the classical specific and diagnostic radiographic features of this disease, which constitutes an uncommon cause of intestinal obstruction, but also can cause bowel ischemia due to prolonged symptoms without a specific preoperative diagnosis.

CASE

A 38-year-old man presented with a 2-week history of recurrent crampy abdominal pain, distension, nausea and infrequent vomiting. He gave no history of abdominal operation. A small bowel followthrough examination showed a cluster of jejuneal segments on the left side of the upper abdomen giving the appearance of an ovoid mass as if contained in a sac (Figure 1). Under fluoroscopic control, manual palpation failed to displace the cluster of bowel loops or change their position. The pelvic cavity showed nearly absent opacified small bowel loops with the cluster of small bowel loops in the left paraduodenal area compressing the left side of an opacified transverse colon on delayed images (Figure 2).

A diagnosis of left paraduodenal internal hernia was made. A confirmatory post-contrast CT study of the abdomen showed an encapsulated cluster or sac-like mass of jejuneal loops between the pancreatic tail and stomach, compressing the transverse colon inferiorly (Figure 3). The inward direction of the mesenteric vessels is seen within the hernia. In both examinations, bowel loops were mildly dilated but gave no evidence of small bowel loop obstruction. Laparoscopic surgery confirmed the presence of a left paraduodenal hernia, which was reduced after excision of the containing sac.

DISCUSSION

Internal hernias present with a variety of symptoms, ranging from vague abdominal pain up to acute intestinal obstruction. Although internal hernias are rare, paraduodenal hernia, also called congenital mesocolic hernias, mesenterico-peritoneal hernias or retroperitoneal hernias, is the commonest.[3,9,10] They result from abnormal rotation of the midgut during embryonic development.[5]

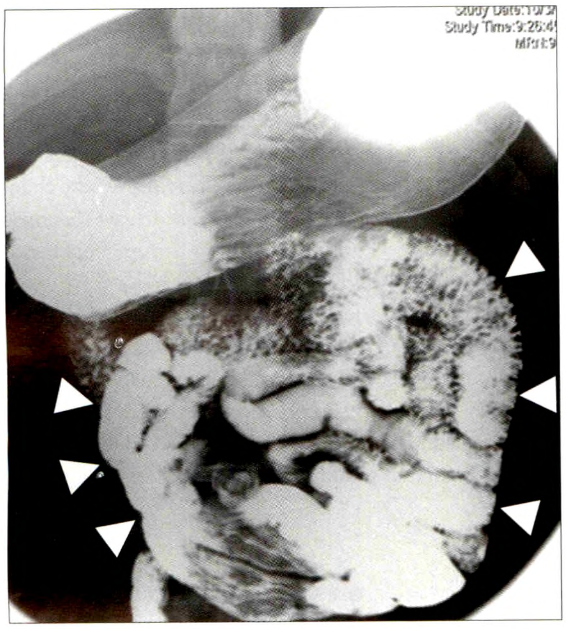

Figure 1. Small bowel followthrough study (SBFT): Cluster of jejuneal loops are seen in an abnormal location in the left upper abdomen giving the appearance of a contained mass (arrow heads).

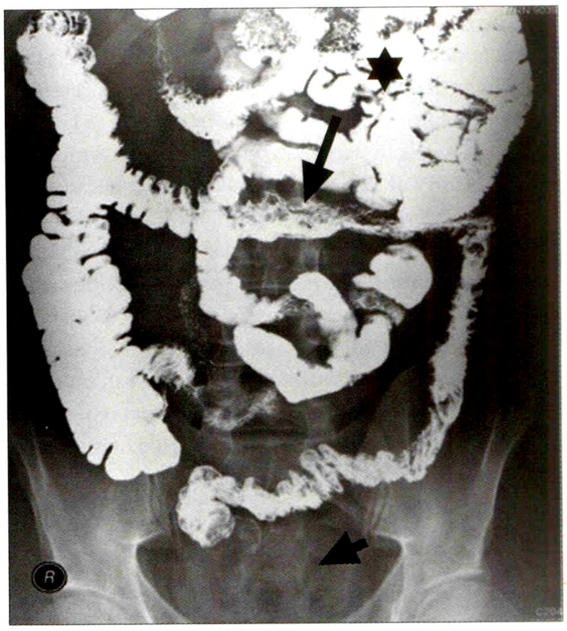

Figure 2. Delayed film of SBFT: The abnormally located small bowel loops (star) are smoothly indenting the transverse colon (long arrow). Note that the pelvic cavity is nearly devoid of small bowel loops (short arrow).

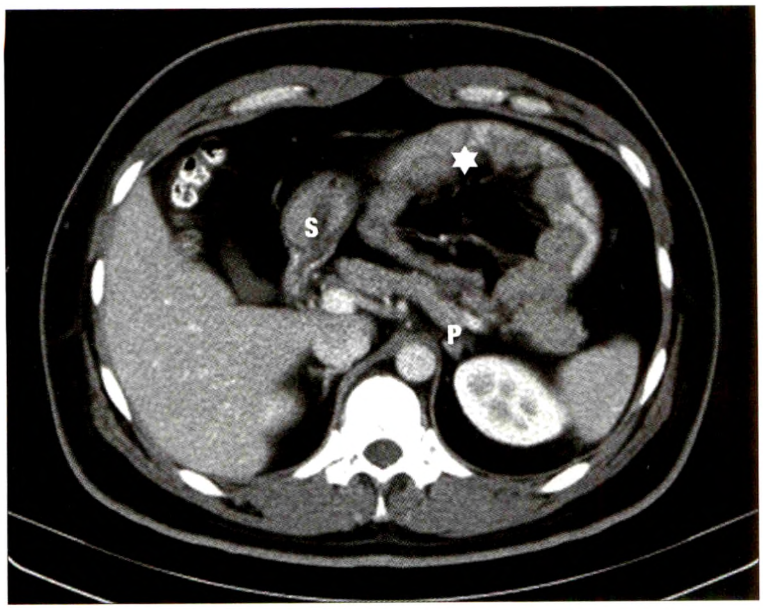

Figure 3. Post-oral and intravenous contrast CT of the abdomen: A circumscribed cluster of small bowel loops (star) are seen anterior to the pancreas (P) and posterior-lateral to the stomach (S), containing inward directed mesenteric vessels (arrow).

The diagnosis of internal hernia is difficult to make before abdominal exploration.[1] These hernias are often difficult to diagnose preoperatively and often present at surgery or autopsy.[1] However, it is important to consider the diagnosis in patients with obstructive symptoms and no history of prior abdominal surgery.[7] Because the clinical diagnosis of internal hernia is difficult, imaging studies such as CT and small bowel followthrough play an important role.[11] In the absence of a specific radiographic diagnosis, internal hernias may not be evident at surgery because they may be inadvertently reduced.[6]

The diagnosis of paraduodenal hernia can be made using small bowel contrast studies.[10] Several reports describe the CT findings of left paraduodenal hernia.[5,8,12,13] However, the bowel loops, on barium study, are seen as an encapsulated circumscribed mass of a few loops of small bowel (usually jejuneal) in the left upper quadrant, lateral to the ascending duodenum. They may have a mass effect, depressing the distal transverse colon and indenting the posterior wall of the stomach[11] plus the absence of small bowel loops in the pelvis gives the characteristic appearance (as in our case), which are diagnostic. CT confirms location and allows proper operative design for correction.

In our case, in the small bowel followthrough study, the appearance of a well-contained small bowel with well circumscribed borders in an abnormal location with an empty pelvis and compression on the transverse colon was diagnostic and it was confirmed by CT, which showed herniated small bowel loops in Landzert's fossa.

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case report

Pemphigus vulgaris in a neonate

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Pemphigus vulgaris (PV) is a common blistering disease in Western countries but neonatal pemphigus (NP) is rare.[1,3,5,6] It is characterized by multiple skin and mucosal erosions and is caused by tranplacental passage of maternal antibodies against desmoglein.[3] It heals spontaneously in two to three weeks.

CASE

A 3-hour-old baby boy was referred with multiple skin erosions on the left side of the neck, upper left chest and groin without oral involvement (Figure 1A). He was born by normal vaginal delivery without complication with an APGAR score of 8 and 9 at 1 and 5 minutes, respectively, and a weight of 2.57 kg. His mother was known to have PV since 1999, which was proven by biopsy and immunofluorescence. The product of her first pregnancy in 1999 was a baby boy with multiple erosions. The first baby was diagnosed with NP based on the results of a skin biopsy and immunofluorescence. The erosions healed spontaneously in two weeks. The mother was treated with prednisone, and later dapsone was added. She went into complete remission. She went off treatment in July 2001 and developed a new flare of PV in June 2005 during her second pregnancy. She was treated with prednisone 40 mg every other day. Physical examination of the second baby showed multiple erosions over the left side of the neck, shoulder and groin. Skin biopsy was refused by the parents and indirect immunofluorescence showed 1:10. He was treated with topical fucidin and 1% hydrocortisone, and discharged three days after delivery in good condition. At the age of four weeks, he had complete clearance (Figure 1B).

DISCUSSION

PV is the most common form of pemphigus.[5] It is usually seen in the fifth decade of life.[2,5] Neonatal PV is a rare disease[1,3,6] seen soon after birth and characterized by cutaneous, mucosal or mucocutaneous erosions. PV is diagnosed by histological and immunofluorescence studies. Routine histology will show epidermal basal cell vacuolization and spongiosis with exocytosis of polymorphonuclear leucocytes and eosinophils. Immunofluorescence will show IgG and C3 deposition. Indirect immunofluorescence is positive in patients with active disease. A high titre indicates active disease.[2] It usually resolves spontaneously in 2 to 3 weeks.[2-5,7,9,12,13,19-21]

Neonatal PV results from transplacental passage of IgG maternal autoantibodies, mainly class 4, against desmoglein 3 (Dsg3), a transmembrane glycoprotein of the cadherin family.[1,3,4,5,7,8,11,20,23-27] More than 21 cases of neonatal PV have been reported (Table 1), with the first proven one in 1975 by Rucco et al.[28] However, there are only 3 reported cases of pemphigus foliaceus (PF).[15-17] This difference in incidence may be related to the distribution of Dsg1 and 3 in neonatal skin. Dsg1, the protein affected in PF, is present throughout the epidermis in both adults and neonates, while type 3 is present in the basal and intermediate suprabasal layer in adults, but throughout the epidermis in neonates. So the frequency of neonatal PF is less than PV in babies born to mothers with pemphigus based on the desmoglein compensation theory.[5,18] This is supported by at least 18 cases of pregnant women with PF who delivered babies free of the disease.[29,30] There is no correlation between the titer of maternal PV antibodies and the presentation of the disease in neonates.[2,5,6] This is supported by cases of neonatal PV from mothers with no active disease[5,9,31] and cases of healthy neonates born to mothers with highly active disease.[4-6,16,17,32-36] The mother might have only oral disease while the baby has both oral and cutaneous involvement.[5,36] Stillbirths have been also reported.[23,24,31]

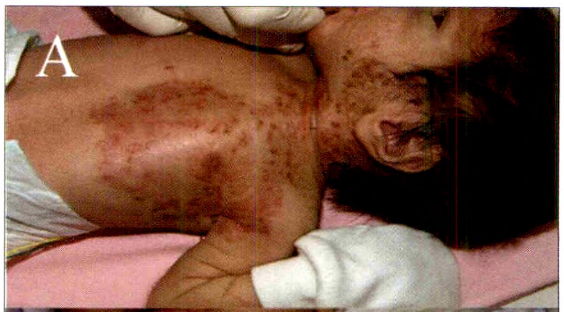

Figure 1a. At birth, multiple eroded vesicles at upper chest and left side of the neck.

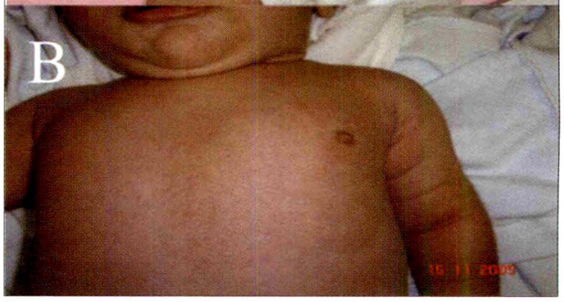

Figure 1b. At age four weeks with complete healing.

Table 1. Reported cases of neonatal pemphigus vulgaris.

Reference number	Mother's Disease	Recovery Duration	Treatment	DIF**	IDIF*	Site	Sex
1	Severe	2 weeks	Like above	IgG and C3	1/160	Skin and oral cavity	F
3	Mild	2 weeks	Emollient and mupirocin	IgG and C3	1/160	Skin and tongue	F
6	Unknown	2 weeks	Like above	NA	NA	Skin	F
7	Mild	2 weeks	Like above	IgG and C3	1/160	Skin	M
8	Unknown	3 weeks	Like above	NA	1/20	Skin	F
9	Mild	2 weeks	No treatment	IgG and C3	1/40	Skin and occipit	M
10	Mild	2 weeks	Emollient and mupirocin	IgG and C3	1:80	Skin	F
12	Severe	2 weeks	No treatment	IgG	1/20	Oral	M
13	Mild	3 weeks	No treatment	NA	1/20	Skin, tongue and scalp	F
15	Unknown	3 weeks	Like above	IgG	1/32	Skin and occipit	M
22	Mild	2 weeks	No treatment	IgG	NA	Skin	F
34	Unknown	2 weeks	Like above	IgG and C3	Neg	Skin and scalp	F

* Indirect immunoflurescence, **direct immunoflurescence, Rx: treatment, NA: Not available, Neg: negative result, M: male, F: female

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case report

Multidrug resistant *Acinetobacter* nosocomial meningitis treated successfully with parenteral tigecycline

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Infections due to *Acinetobacter* are increasingly identified, most commonly during hospitalization. *Acinetobacter baumannii* is a gram-negative pathogen that targets immunocompromized patients. It is involved less frequently in outpatient health care infections.[1,2]

Catheter-associated blood stream infection (CA-BSI) due to *Acinetobacter* is relatively uncommon, but causes morbidity and extra costs.[3] In several publications, it was found to rank fifth to tenth among pathogens isolated in intensive care units causing CA-BSI[4-7] and is associated with a crude mortality of 43.4%.[4] Lower respiratory tract infections created by nosocomical *Acinetobacter* frequently occur as an outbreak, especially in ventilated patients, causing ventilator-associated pneumonia (VAP).[2] Surgical site infection (SSI) due to *Acinetobacter*, though uncommon, does occur and is increasing in frequency. In a published study, *E. coli* and *Enterobacter* isolates were significantly less commonly reported than *Acinetobacter* isolates ($P<.001$), but *Acinetobacter* comprised only 2.1% of the isolates in 2003[8]. In a retrospective chart review of data from over 16 years, a study from Japan reported that *Acinetobacter* was not found to cause ventriculo-peritoneal shunt infection in adult and pediatric age groups, none of whom had an external CSF drain (cranial or lumbar).[9]

CASE

A 26 year-old male patient was admitted in January 2007 to the Specialty Hospital, Amman, Jordan. He presented with a history of motor vehicle accident in which he sustained multiple injuries to the head, face and extremities. On admission his vitals were: pulse rate 84/minute, blood pressure 115/70 mm Hg, and he was afebrile. He was on a ventilator with multiple trauma to the mouth, right ear, maxillae, mandibles and eyes. His chest examination showed good bilateral air entry, the abdomen was soft, and diagnostic peritoneal lavage was negative. His extremities, neck and back showed skin abrasions. He was unconscious, with reactive pupils—right more than left, and no spontaneous movements. His serum creatinine and electrolytes were normal, and stayed normal all through his illness. SGPT was 100 IU/L, LDH 392 IU/L, and both normalized later. Hemoglobin was 13.2 g/dL on admission, 11.1 g/dL the next day and remained as such until discharge. Several blood cultures as well as urine cultures were sterile. His chest X-ray and cervical spine X-ray showed no abnormality. CT of the brain showed subarachnoid hemorrhage and a basal skull fracture.

On admission he was started on vancomycin and ceftriaxone for a few days. Two days later a percutaneous endoscopic gastrostomy was placed and a lumber external drain was inserted because of evidence of increasing intracranial pressure. Three days later facial reconstructive surgery was done. On the fourth day he became febrile with right lung collapse and an infiltrate. He was started on pipracillin/tazobactam 4.5 g intravenously every 8 hours and amikacin 1 g infusion over one hour once daily. CSF analysis showed WBC 3200/mm^3, polymorphonuclear lymphocytes 27%, lymphocytes 73%, RBC 70/mm^3, glucose 45 mg/dL, protein 60 mg/dL, and culture showed multidrug resistant (MDR) *Acinetobacter*. Subsequent serial CSF cultures 5 and 7 days later grew MDR *Acinetobacter*. The lumbar drain was removed and some clinical improvement was noted. A week later he became confused and febrile with headache; his CSF analysis showed WBC 4300/ mm^3, polymorphs 94%, sugar 55 mg/dL, protein 162 mg/dL, and the culture again showed MDR *Acinetobacter*. He was started on tigecycline monotherapy. While on treatment he had periodic CSF evaluations including gram stains and cultures, each of which were incubated for 5 days in thioglycolate (Table 1). Two days later his

Table 1. CSF evaluations while on tigecycline monotherapy by date.

	29/1	5/2	7/2	15/2	17/2	19/2	21/2	24/2	3/3
WBC /mm³	3200	NA	NA	4300	280	20	70	30	30
P%	27	NA	NA	94	27	7	8	4	4
L%	73	NA	NA	6	73	90	89	96	96
Glucose mg/dL	45	NA	NA	55	45	60	31	54	52
Protein mg/dL	60	NA	NA	162	186	36	50	62	37
Gram stain	NA	NA	NA	GNB	None	GNB	None	None	None
Culture	NA	Ac	Ac	Ac	NG	NG	CoNS	NG	NG
RBc / mm³	70	NA	NA	20	20	0	0	0	10

NG = No growth, Ac = MDR Acinetobacter calcoaceticus, P%= Neutrophils, L% = Lymphocytes, MDR = Multidrug resistant, GNB = Gram-negative bacilli, CoNS= Coagulase-negative Staphylococci, NA= Not Available

WBCs became 280/mm³ with polymorphs 27%, and lymphocytes 73%. The culture was sterile.

Two days later he regained consciousness, with resolution of confusion. The lumber external drain (which stayed for 10 days) was removed. He was continued on tigecycline during his illness and the external drain was removed without the need for a permanent shunt. Coagulase-negative staphylococcus grew later from the cerebrospinal fluid culture; it was interpreted as a contaminant.

DISCUSSION

In the last few years the prevalence of MDR *Acinetobacter* has increased, thus narrowing the therapeutic options. Colomycin has been reintroduced recently as the best option for the treatment of MDR *Acinetobacter* bacteremia. It has also been described in the treatment of ventilator-associated pneumonia as a parenteral agent or in combination with the inhaled form, with good results.[10] Previously, the side effects of colomycin were exaggerated; more recent evaluations indicate its side effects are less serious than once believed. Nephrotoxicity still occurs, but neurotoxicity is exceedingly rare in recent experience.[10,11]

However, newer agents are now available that may add to the treatment armamentarium against MDR *Acinetobacter*. Tigecycline is a relatively new FDA-approved antimicrobial for use in complicated skin and skin structure infections, and complicated intra-abdominal infections, in which polymicrobial infections are likely.[12,13] It also may be used in cases where deep tissue penetration is needed, or where multi-drug resistant pathogens are suspected.[16,17] Tigecycline has good in vitro activity against imipenem-resistant *Acinetobacter*, showing 100% sensitivity.[18,19]

Our patient had a lumbar shunt infection causing meningitis with MDR *Acinetobacter*, which took place during a limited outbreak in the hospital. Due to the difficulty in obtaining colomycin (not registered in Jordan), and the recent availability of tigecycline, the patient was started on the latter antimicrobial.

Tigecycline is the first known glycylcycline. A minocycline derivative, its formula modification enables it to overcome major mechanisms of resistance in the parent tetracycline compounds. i.e., tetracycline-specific efflux pump acquisition and ribosomal protection.[14-17] Its antibacterial spectrum covers aerobic and anaerobic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *enterococci* (VRE), and penicillin-resistant *Streptococcus pneumonia* (DRSP),[15,16] as well as extended-spectrum beta-lactamase (ESBL) gram-negative bacteria. Tigecycline is a safe drug for use in treating infections for extended periods of time (up to several months) without experiencing major significant organ toxicity.[20]

Among the non-fermentative gram-negative bacilli such as *Pseudomonas aeruginosa*, tigecycline activity is poor (16% susceptibility), but it is very active against *Acinetobacter* species (96.1% susceptibility at a concentration of ≤4 mg/L) and *Stenotrophomonas maltophilia* (100% susceptibility).[15,16,21] Also it covers "atypical" pathogens. Tigecycline is rapidly distributed and has a large volume of distribution, indicating extensive tissue penetration, and it exhibits time-dependent killing with a post-antibiotic effect (PAE).[17]

In a rabbit model of meningitis, a single dose of tigecycline of 120 mg/kg yielded concentrations in CSF of 11 µg/mL at 3 hours that stayed at a steady level or increased at 6 hours.[15,22] A review of the literature found no information on tigecycline and CSF levels in humans, in either healthy or inflamed meninges.

Our patient was started on tigecycline 50 mg intravenously twice daily (recommended loading dose, 100 mg). He showed remarkable improvement with subsidence of fever, headache and confusion. On the seventh day the lumbar drain was removed, and he showed continued improvement. Repeat CSF analysis and cultures showed remarkable improvement, though during his treatment course he grew coagulase-negative staphylococci (Table 1). Whether this microbe was a contaminant or a secondary pathogen, it disappeared during treatment with tigecycline. Tigecycline was continued for 21 days, until a week after the last sterile CSF culture. A longer duration of treatment was not deemed necessary, due in part to the rapid and excellent clinical and microbiological response early in the treatment course. The patient was discharged a few days after stopping the treatment. When followed up as an outpatient he was healthy, with no symptoms referred to the previous nosocomial meningitis. In reviewing the literature, I found no other published case for a patient treated with tigecycline for nosocomial meningitis, or external shunt-related meningitis. Controlled trials are needed for this indication, especially since shunt infection is not uncommon.

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Overweight and obesity among attendees of primary care clinics in a university hospital

To the Editor: Obesity is a rapidly escalating problem in modern society. It has a complex genetic, environmental and behavioral etiology for which there is no simple, or single solution.[1] The WHO estimated that by 2020 noncommunicable diseases will become the principal global causes of morbidity and mortality.[2] Obesity is a risk factor for several chronic diseases, including hypertension, dyslipdemia, diabetes, cardiovascular diseases, sleep apnea, and osteoarthritis.[3] Obesity levels have risen sharply in Australia, the USA, Canada and Europe.[1,2] In Australia over 65% of men and 53% of women are overweight or obese.[1] In 2000, 64.5% of American men and women were overweight, of which 30.5% were obese.[4] However, recent reviews have reported significant increases in the prevalence of overweight and obese individuals in developing countries.[2,5] Obesity is an epidemic all around the world, including Saudi Arabia.[6-11]

The National Epidemiological Household survey was conducted more than 10 years ago for the purpose of studying the prevalence of overweight and obesity among Saudi subjects over the age of 15 years in different regions of Saudi Arabia.[12] The survey showed a high prevalence of overweight and obesity among Saudi subjects. The prevalence of overweight among male subjects was significantly higher than for female subjects (29% vs. 27%), and the prevalence of obesity among female subjects was significantly higher than for male subjects (24% vs. 16%). Another National Epidemiological Health survey was conducted between 1995 and 2000.[13] This community-based survey showed an alarmingly high prevalence of metabolic syndrome in Saudi Arabia. Metabolic syndrome increases the burden of coronary artery diseases and other disorders.[13]

Saudi Arabia has gone through significant changes in nutritional and lifestyle habits over the last four decades. Such changes are expected to have an impact on the magnitude of chronic diseases in the society, among them, obesity.[10,12]

The present cross-sectional study was designed to estimate the prevalence of overweight and obesity among males and females attending primary care clinics at King Khalid University Hospital in Riyadh, Saudi Arabia over a one-month period from 22 April to 22 May 2006. All males and females patients attending the primary care clinics were included in the study. Any patient who could not stand on the scale because of a handicap was excluded. Weight and height for both males and females patients were taken by 11 nurses working under the supervision of the 2 head nurses. The average number of clinics was 6 in the female section and 5 in the male section. The data recorded by the nurses included hospital number, sex, age, weight, and height. Body mass index (weight in kilograms divided by height in meters squared) was defined as shown in Table 1. Data were analyzed using the Statistical Package for Social Science (SPSS) version 11.5 and a *P* value less than 0.05 was considered statistically significant. Of the 3 205 adult patients, 40% were male and 60% were female. Table 1 shows BMI by age group and sex, indicat-

Table 1. Age, sex and body mass index in 3205 adult patients attending primary care clinics.

Body mass index	Normal (< 25)	Overweight (25 to <30)	Obesity class 1 (30 to <35)	Obesity class 2 (35 to <40)	Morbid obesity (≥40)	Total	*P* value
	N (%)*	N (%)*	N (%)*	N (%)*	N (%)*		
Age (years)							.0001
12 to <20	161 (60.3)	50 (18.7)	31 (11.6)	16 (6)	9 (3.4)	267	
20 to <40	254 (26)	298 (30.5)	234 (24)	102 (10.4)	89 (9.1)	977	
40 to <60	142 (9.5)	453 (30.4)	463 (31.1)	274 (18.4)	159 (10.7)	1491	
≥60	79 (17)	167 (36)	127 (27.4)	65 (14)	26 (5.6)	464	
Sex							.0001
Male	297 (23.2)	511 (40)	303 (23.7)	110 (8.6)	58 (4.5)	1279	
Female	341 (17.7)	459 (23.8)	553 (28.7)	347 (18)	226 (11.7)	1926	
Total	638 (19.9)	970 (30.3)	856 (26.7)	457 (14.3)	284 (8.9)	3205	

* Percentage by BMI category.

ing statistically significant differences between groups.

Variance prevalence rates between the National Community Survey and the present study might be explained because the current study was done in hospital based primary care setting, which might limit generalization of the result to the community, or because the prevalence of overweight and obesity has increased during the last decade as the national survey was done more than 10 years ago. The rapid socioeconomic development during the past four decades in Saudi Arabia has been accompanied by lifestyle changes where high calorie diet and diminished physical activity are the fundamental components of lifestyle contributing to an increased prevalence of obesity and associated diseases.[10,12] Other studies done at primary care centers to determine the prevalence of obesity among Saudi males in the Riyadh region during May and June 1994 showed that only 36.6% of Saudi males were their ideal weight (BMI <25), while 34.8% were overweight (BMI=25-29.9), 26.9% were moderately obese (BMI=30-40), and 1.7% were morbidly obese (BMI >40).[6] A cross-sectional study of 1385 Saudi females attending 15 health centers in urban and rural areas in the Riyadh region conducted during September and October 1992 showed that only 26.1% of subjects were their ideal weight (BMI <25), while 26.8% were overweight (BMI 25-29.9), 41.9% were moderately obese (BMI 30- 40), and 5.1% were morbidly obese (BMI >40).[7] Bad dietary habits, such as eating high fat/high energy food can contribute to obesity in adolescence, which tends to persist into adulthood. A cross-sectional study to determine the level and sources of knowledge about foods and healthy diets among male and female adolescents in the Al-Khober Area, eastern province of Saudi Arabia, showed that knowledge of healthy diets among school students was inadequate, and that the main sources of knowledge about health and disease reported by the male and female respondents were television (58% and 61%, respectively), magazines (31% and 39%) and the daily news paper (33% and 34%). Primary health care center staff were the least source of knowledge (17% and 16%). The study recommended that health education and information about healthy eating habits and lifestyle be included in school curricula.[14]

Successful management of overweight and obesity depends on a systematic approach. Consistent use of such a system identifies patients who would benefit from nutritional counseling, because the behaviors that increase a patient's risk for related morbidity and mortality are rarely what bring a patient to the clinic. That is, patients rarely present with the complaint that they have trouble eating a healthy diet. They are more likely to present with the sequelae of poor nutrition, such as weight gain, or even with symptoms of diabetes mellitus, or a routine evaluation may detect increased blood pressure or an elevated low density lipoprotein (LDL) cholesterol level. An approach that includes a system for assessing behavioral risk factors, especially when such conditions are present, is essential. In addition, the use of such an approach conveys to the patient that his or her physician takes proper nutrition and adequate physical activity seriously as components of a health- promoting lifestyle. The process of care (including the patient-physician relationship) and the systems that support it can improve the quality of care.[4]

In conclusion, family physicians have a key role and responsibility in preventing overweight in the community, and helping obese patients to loss weight and improve their health.

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Preoperative nutritional parameters in children with congenital heart diseases under two years of age

To the Editor: Congenital heart diseases (CHD) may affect the growth of children and lead to malnutrition. The speed of growth is more rapid during the first three years and nutritional needs are greatest at this point. These years are a critical period for future cognitive ability. The treatment of emergency problems in children with CHD needing surgery are a priority, but nutritional restoration usually does not take place in these protocols.

In the preoperative period, 24 children with CHD hospitalized for cardiac or secondary pulmonary problems were evaluated. Subjects were children younger than two years of age. Z-scores for weight and height were calculated using data from percentile charts for Turkish children. Wasting criteria, stunting criteria and Wellcome scores were used to evaluate nutritional status. Waterlaw's scores define the stages of acute and chronic nutritional status and include growth stunting and wasting. Cyanotic and non-cyanotic cases were compared. Half of the patients were female. The average birthweight was 2932±603 gram, the average age was 10.19±1.12 months, weight was 5951±2201 grams and height was 63.7±8.5 centimeters. Of these cases, 21 had a normal birthweight for gestational age and three had low birthweight. When we evaluated the patients for protein-energy malnutrition, the severely acute malnutrition ratio with wasting was 66.6% and chronic malnutrition according to growth stunting was 83.3%. Out of 24 patients, 33.3% (n=8) were diagnosed with marasmus by Wellcome scores (Table 1).

Malnutrition is the most important risk factor in mortality and morbidity in childhood. It affects life quality of children negatively. Its detection and treatment are important components in the clinical management of many conditions.[1] We also believe that the nutritional evaluation of children with CHD is often ignored during the first admission. Hornbya et al suggest that incorporating simple anthropometric and functional measurement into protocols of nutritional assessment for patients with CHD can identify patients at risk.[1]

Cardiac malformations may be responsible for malnutrition and the degree of malnutrition is related to hemodynamic status.[2] Based on these data, children with CHD were classified as cyanotic or non-cyanotic. Chronic malnutrition is a common and serious problem in infants with CHD and was more common in cyanotic patients (92.3%) than in non-cyanotic patients (72.7%). Nearly all of the cyanotic patients were affected by acute and chronic malnutrition and their Z-scores for both weight and height were under −2 SD. Chronic malnutrition was more severe in children with CHD below 2 years of age.[3] Daily energy expenditure was also higher in children with CHD between 2 and 8 months of age.[4]

In some studies, symptomatic infants (73%) had higher rates of chronic malnutrition than asymptomatic infants (46%) and the percentile scores of cyanotic CHD patients were lowest.[5] Among children hospitalized with CHD, the rates of acute and chronic malnutrition were 33% and 64%, respectively.[6] In patients with cyanotic CHD and/or congestive heart failure (CHF), acute or chronic malnutrition occurs in 70%. The rate was 30% among noncyanotic patients without CHF.[6] In our study, it was determined that the younger the patients were, the worse their malnutrition. In another study, hypoxia and pulmonary hypertension were the most important addictive fac-

Table 1. Nutritional parameters in hospitalized children with congenital heart disease before surgery.

	Total (n=24)	Cyanotic group (n=13)	Non-cyanotic group (n=11)
Waterlaw's Criteria:			
Wasting			
Severe malnutrition	66.6 (16)	69.2 (9)	63.6 (7)
Moderate malnutrition	16.6 (4)	15.4 (2)	18.2 (2)
Mild malnutrition	4.2 (1)	0	9.0 (1)
Normal	12.5 (3)	15.4 (2)	9.0 (1)
Stunting			
Chronic malnutrition	83.3 (20)	92.3 (12)	72.7 (8)
Wellcome Scores			
Underweight	45.8 (11)	38.5 (5)	54.5 (6)
Marasmus	33.3 (8)	46.2 (6)	18.2 (2)
Kwashiorkor	0	0	0
Normal	20.8 (5)	15.4 (2)	27.2 (3)

Data are percentage and number of patients.

tors for growth failure and malnutrition.[2]

According to our results using Wellcome scores, 46.2% of the cyanotic group had marasmus and 38.5% were underweight. As shown, infants under 2 years of age with CHD needing an operation had malnutrition in different degrees and if they were cyanotic, malnutrition was worse. The adverse effects of hospitalization on nutritional status were shown in undernourished children.[7,8] This effect was highest between 2 and 6 years (32%).[7] In different studies, rates of malnutrition have been reported in 30% to 50% of hospitalized children.[9] Nutritional support reduces the time of hospital stay in patients with critical illness.[10] Because of the hospital stay, the life quality of mothers was reduced and breastfeeding was affected. Of our patients, 66.6% were breastfeeding. It is clear that special attention should be given to children under 2 years of age in whom surgery is planned. Nutritional support should be added after the first emergency therapy.

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Probable montelukast-induced hepatotoxicity in a pediatric patient: case report

To the Editor: Drug-induced liver injury is a potential complication of many medications. Montelukast and zafirlukast are competitive and selective leukotriene-receptor antagonists (LTRA) approved for the prophylaxis and chronic treatment of asthma in pediatric patients and adults. These LTRA are usually well tolerated. Montelukast is extensively metabolized by the hepatic microsomal cytochrome P450 3A4 and 2C9.[1] Hepatotoxicity has been associated with not only zafirlukast, but recent reports have also described elevated liver enzyme levels, hepatitis, and fulminant hepatic failure induced by montelukast.[2-8] However, all the described cases are adult patients and there have been no similar reports with montelukast in children. We present a patient who we believe is the first pediatric case of acute hepatitis while receiving montelukast.

A 5-year-old boy was admitted to our hospital with fatigue, nausea, vomiting and abdominal pain. The patient had a history of chronic bronchial asthma. He had been prescribed montelukast at a 5 mg daily dose for the last 2 years. On physical examination, he was not icteric, the abdomen was nontender, and no hepatosplenomegaly or ascites were present. Examination of other systems were normal. At presentation, the aspartate aminotransferase (AST) level was 990 IU/L (normal, 15 to 55 IU/L), the alanine aminotransferase (ALT) level was 658 IU/L (normal, 5 to 45 IU/L), the glutamyltranspeptidase level was 145 IU/L (normal, 5 to 32 IU/L), the total bilirubin level was 2.8 mg/dL, the indirect 0.7 mg/dL, the direct 2.1 mg/dL, and the ALP level was 445 IU/L (normal, 45 to 420 IU/L). The hepatic synthetic function was intact as indicated by a normal serum albumin level and PT. An abdominal ultrasound showed normal hepatic morphology. Viral serologic tests were negative.

There was no history of using other drugs, no risk factors for exposure to parenterally transmitted viruses or other hepatotoxins, and no family history of liver disease. Montelukast was discontinued with the development of symptoms. AST, ALT, bilirubin, ALP, and glutamyltransferase levels normalized within two weeks. Montelukast-induced hepatitis was suggested by rapid improvement after dechallenge, the exclusion of other causes of hepatitis and by comparison with the reports of similar cases. A liver biopsy had not been done.

Using LTRA in the treatment and prophylaxis of allergic asthma in childhood is gradually becoming more prevalant. The side effects of montelukast have rarely been reported, except for sporadic cases of urticaria, angioedema, erythema nodosum, and Churge-Strauss syndrome in adults.[9,10] One patient presented with pemphigus after using montelukast.[11] Recently, several cases of hepatotoxicity with zafirlukast and rarely, montelukast, were reported, but none included pediatric patients.

The mechanism of hepatotoxicity associated with LTRA is not clearly defined. Not infrequently drug-induced hepatotoxicity appears after a latency period as long as 2 years,[7] but the reported cases related to montelukast and zafirlukast had latency periods between 5 to 24 months.[2,3,6,7] This pattern may be similar to phenprocoumon-induced hepatitis, which has a latency period of typically 6 months and more.[7] This phenomenon is still not fully described. Besides this, other mechanisms of hepeatotoxicity, like hepatotoxic metabolites, idiosyncrasy, drug reactions and immunologic mechanisms are hypothesized.[2,8] In liver biopsy, histological findings from previously published reports described *mild* chronic inflammation in portal areas , without lobular inflamation or fibrosis.[8]

Clinical trials of montelukast showed no significant difference in liver function abnormalities between the montelukast group and the placebo group (2.1% of 1955 montelukast recipients had an increased ALT level vs. 2.0% of 1180 placebo recipients, and 1.6% of montelukast recipients developed self-limited, transient increases in AST levels vs. 1.2% of placebo recipients).12 To our knowledge, this is the first reported case of drug-induced hepatitis probably caused by montelukast in a child.

A review of all reported cases of leukotriene modifier-induced hepatitis revealed that hepatic toxicity may develop within weeks or as late as 24 months after initiating therapy.7,8 With the increasing use of these drugs, which has coincided with monitoring of liver function, more asymptomatic cases may come on the scene. Because of their efficacy, convenient oral dosing and apparent safety, the LTRA, montelukast and zafirlukast, have become frequently prescribed drugs for the therapy of asthma. To date, serial liver function testing is not recommended for patients receiving zafirlukast or montelukast,2,8,13 but physicians should be aware of a potential hepatotoxic effect of montelukast, which may occur after many months of drug initiation. Periodic screening of liver function tests seems like a more prudent approach.

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Arab and Muslim Physicians and Scholars

Ibn Al-Haytham: Father of Modern Optics

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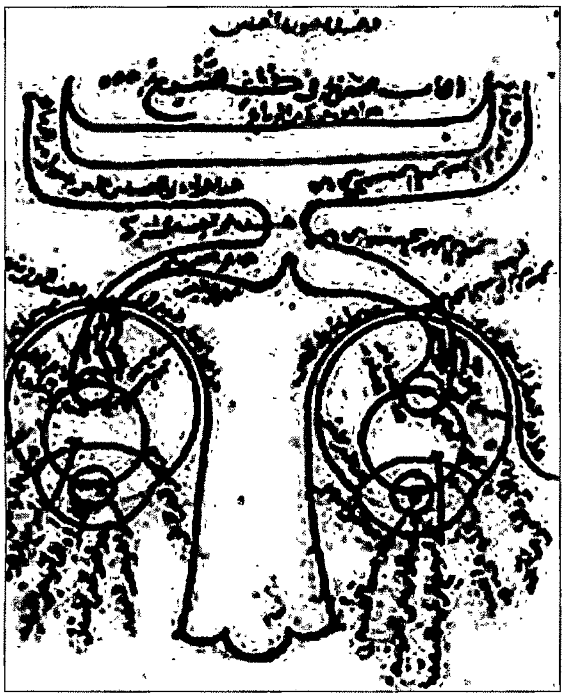
The Arab Muslim scholar Abu Ali al Hasan ibn al-Haytham , known in the west as Alhacen or Alhazen was born in 965 in the city of Basra in Southern Iraq, hence he is also known as Al-Basri.[1] He was educated in Basra and Baghdad, and died in Cairo, Egypt in the year 1040.[2]

Many details of the life of Ibn al-Haytham have been lost over time. The stories related to his life are often contradictory, depending on the historian relating them. Most of the data on the biography of Ibn al-Haytham came from the writings of the thirteenth century Muslim historian Ibn al-Qifti (1172-1248). Initially, Ibn al-Haytham was trained for a civil service job and was appointed as a judge for Basra. Due to the presence of various religious movements with diverse and conflicting views at that time, he became disillusioned with religious studies and decided to dedicate his time and effort for the study of science. His knowledge in mathematics and physics became legendary and he was well known in Iraq, Syria and Egypt. He was invited by Al-Hakim bi-Amr Allah, the Fatimid Caliph of Egypt to help in regulating the flow of the Nile during the floods. Al-Hakim, a Shiite of the Ismaili sect, was known to be an eccentric ruler who issued several arbitrary edicts and laws, prohibiting the consumption of certain foods, preventing women from leaving their homes, killing all the dogs, and forcing people to work during the night and rest by day. He was quite brutal and had killed his tutors and ministers on a whim. When Ibn al-Haytham realized on his field work along the Nile that his scheme to regulate the Nile's water flow by building a dam south of Aswan was impractical, he feared for his life. To avoid the potential of the deadly wrath and anger of his temperamental and mentally unstable patron, he faked insanity. He was stripped of his possessions and books, and was kept under house arrest for about 10 years until the time of Al-Hakim's death in 1021, when he was assassinated in mysterious circumstances.



Original image, Diagram of the Eyes and Related Nerves, from Kitab al-Manazir (Book of Optics) by Ibn al-Haytham, Istanbul, Eleventh Century.

Following his release from house arrest, he lived in a domed building (Qubbah) close to the Azhar Mosque in Cairo, teaching mathematics and physics, writing science texts, and making money by copying texts.[3]

During his period of incarceration, he wrote his influential *"Kitab Al Manazer"* or the Book of Optic, in addition to several significant books and chapters on physics, mathematics, engineering, astronomy, medicine, psychology, anatomy, visual perception and ophthalmology. He wrote his introduction of the scientific methods.[4]

Ibn al-Haytham was a prolific author. He wrote more than 200 works on a wide range of subjects, of which at least 96 of his scientific works are known, and approximately 50 of them have survived to date. Nearly half of his surviving works are on mathematics, 23 of them are on astronomy, and 14 of them are on optics, with a few on other areas of science.[5] Not all of his surviving works have yet been studied, but some of his most important ones are described below. These include:

- *Kitab Al Manazer* (Book of Optics)
- *Risalah fi al-Dawa'* (Treatise on Light)
- *Mizan al-Hikmah* (Balance of Wisdom)
- *Maqalah fi al-Qarastun* (Treatise on Centers of Gravity)
- *Risalah fi al-Makan* (Treatise on the Place)
- *Al-Shukuk al Batlamyus* (Doubts concerning Ptolemy)
- On the Configuration of the World
- The model of the Motion of the Seven Planets

Scientific Method

Elements of modern scientific methods are found in early Islamic philosophy, in particular, using experiments to distinguish between competing scientific theories, and a general belief that knowledge reveals nature honestly. Islamic philosophy developed in the Middle Ages and was pivotal in scientific debates. The key figures for these debates were scientists and philosophers. Ibn al-Haytham was quite influential in this regard. An important observation in his book *"Kitab Al Manazer"* led him to propose that the eyes receive light reflected from objects, rather than emanating light themselves, contradicting contemporary beliefs, including those of Ptolemy and Euclid. The way in which Ibn al-Haytham combined observations and rational arguments had a great influence on Roger Bacon and Johnnes Kepler in particular. Bacon (1214-1296), a Franciscan friar working under the tuition of Grosseteste, was inspired by the writings of Ibn al-Haytham, who preserved and built upon Aristotle's portrait of introduction.

Ibn al-Haytham developed rigorous experimental methods of controlled scientific testing in order to verify theoretical hypotheses and substantiate inductive conjectures. Ibn al-Haytham's scientific method was very similar to the modern scientific method and consisted of a repeating cycle of observation, hypothesis, experimentation, and the need for independent verification.[5,6]

Gorini wrote the following on Ibn al-Haytham's introduction of the scientific method: "According to the majority of the historians, al-Haytham was the pioneer of the modern scientific method. With his book, he changed the meaning of the term "optics", and established experiments as the norm of proof in the field. His investigations were based not on abstract theories, but on experimental evidences. His experiments were systematic and repeatable".[7]

Physics and Optics

Ibn al-Haytham's theory of light and vision is neither identical with nor directly descendant from any one of the theories known to have previously existed in the antiquity or in Islam. The first real appreciation of the action of a lens, in particular the ability of a convex form to produce a magnified image of an object, appears to be credited to Ibn al- Haytham.[8,9] It was not until the late 13th century that spectacles were invented, representing the first practical use of magnification in society.[9,10] Ibn al-Haytham made a thorough examination of the passage of light through various media and discovered the laws of refraction. He also carried out the first experiments on the dispersion of light into its constituent colors. Ibn Al-Haytham's seven volume treatise on optics, *Kitab al-Manazer* (Book of Optics), which he wrote while incarcerated between 1011 to 1021, which has been ranked alongside Isaac Newton's *Philosophiae Naturalis Principia Mathematica* as one of the most influential books ever written in physics, drastically transformed the understanding of light and vision.[8,9]

He dealt at length with the theory of various physical phenomena like shadows, eclipses, the rainbow, and speculated on the physical nature of light. He also attempted to explain binocular vision, and gave a correct explanation of the apparent increase in size of the sun and the moon when near the horizon. He is known for the earliest use of the camera obscura and pinhole camera.[11] As stated above, he contradicted Ptolemy's and Euclid's theory of vision that objects are seen by rays of light emanating from the eyes; according to him the rays originate in the object of vision and not in the eye.

Structure of the eye, by Ibn al-Haytham, from the Book of Optics.

Through these extensive researches on optics, he has been considered as the father of modern optics.

In addition to the Book of Optics, Ibn al-Haytham wrote a supplement entitled *"Risala fi l-Daw"* (Treatise on Light). This supplement contained further investigations on the properties of luminance and its radiant dispersion through various transparent and translucent media. In his treatise, *Mizan al-Hikmah* (Balance of Wisdom), Ibn al-Haytham discussed the density of the atmosphere and related it to altitude. He also studied atmospheric refraction. His optical writings influenced many Western intellectuals such as Roger Bacon, John Pecham, Witelo, and Johannes Kepler.[11,12,13]

Astronomy

While not counted among the greatest Arab astronomers, his works show that he had mastered the techniques of Ptolemaic astronomy. Some of these works also reveal his ability to solve the problems that received attention from Arab astronomers, such as determining the Qiblah (direction of prayer). His critique of Ptolemaic planetary models, as presented in the *Almagest* and *Planetary Hypotheses*, appears to have inspired research that led to their replacement by non-Ptolemaic arrangements in the 13th century Maragha and 14th century Damascus. This astronomical work was written between 1025-1028 *"Al-Shukūk 'alā Batlamyūs"*, and then translated as *Doubts concerning Ptolemy* or *Aporias against Ptolemy*.[14] He considered that some of the mathematical devices Ptolemy introduced into astronomy, especially the equant, failed to satisfy the physical requirement of uniform circular motion.[14]

Astronomers of the European Renaissance were influenced by his work *"On the Configuration of the World"*, where he continued to accept the physical reality of the geocentric model of the universe, presenting a detailed description of the physical structure of the celestial spheres: "The earth as a whole is a round sphere whose center is the center of the world. It is stationary in its [the world's] middle, fixed in it and not moving in any direction nor moving with any of the varieties of motion, but always at rest".[15]

Ibn al-Haytham's *The Model of the Motions of Each of the Seven Planets*, written in 1038, was an important book on astronomy. The surviving manuscript of this work has only recently been discovered, with much of it still missing, hence the work has not yet been published in modern times. His reform excluded cosmology, as he developed a systematic study of celestial kinematics that was completely geometric. This in turn led to innovative developments in infinitesimal geometry.[16]

Mathematics

In mathematics, Ibn al-Haytham built on the mathematical works of Euclid and Thabit ibn Qurra, and went on to systemize infinitesimal calculus, conic sections, number theory, and analytic geometry after linking algebra to geometry. His contribution to mathematics was extensive. He developed analytical geometry by establishing linkage between algebra and geometry. He studied the mechanics of motion of a body and was the first to maintain that a body moves perpetually unless an external force stops it or changes its direction of motion. This is strikingly similar to the first law of motion described centuries later by Isaac Newton.

His work on catoptrics in *Book V* of the *Book of Optics* contains the important problem known as *Alhazen's problem*. It comprises drawing lines from two points in the plane of a circle meeting at a point on the circumference and making equal angles with the normal at that point. This leads to an equation of the fourth degree. This eventually led Ibn al-Haytham to derive the earliest formula for the sum of fourth powers; and by using an early proof by mathematical induction, he developed a method for determining the general formula for the sum of any integral powers. This was fundamental to the development of infinitesimal and integral calculus.[17]

In geometry, Ibn al-Haytham developed analytical geometry by establishing the linkage between algebra and geometry. Ibn al-Haytham also discovered a formula for adding the first 100 natural numbers.

His contributions to number theory include his work on perfect numbers. In his Analysis and Synthesis, Ibn al-Haytham was the first to realize that every even perfect number is of the form 2^{n-1} (2^n-1) where 2^n-1 is prime, but he was not able to prove this result successfully. It was proved later on in the 18th Century by Euler.[17]

Medicine and Psychology

Ibn al-Haytham was the first to describe accurately the various parts of the eye and give a scientific explanation of the process of vision. In medicine and ophthalmology, Ibn al-Haytham made important advances in eye surgery, and he studied and correctly explained the process of sight and visual perception for the first time.[18,19] He described in detail the various parts of the eye and introduced the idea that objects are seen by rays of light emanating from the objects and not the eyes, as was popularly believed. "Sight perceives the light and color existing on the surface of the contemplated object. Vision perceives necessarily all the objects through supposed straight lines that spread themselves between the object and the central point of the sight".[10]

Ibn al-Haytham is considered by some to be the founder of psychophysics and experimental psychology, for his pioneering work on the psychology of visual perception.[20]

Philosophy

In philosophy, Ibn al-Haytham is considered a pioneer of phenomenology. He articulated a relationship between the physical and observable world and that of intuition, psychology and mental functions. His theories regarding knowledge and perception, linking the domains of science and religion, led to a philosophy of existence based on the direct observation of reality from the observer's point of view. Much of his thought on phenomenology was not further developed until the 20th century.[21] In fact, he is well known to have articulated a comprehensive theory of knowledge.[22]

Ibn al-Haytham is said to have been a supporter of the Asha'ri school of Islamic theology, and opposed to the teachings of the Mu'tazili school, though he may have been a Mu'tazili supporter himself at some point in his life.

Finally, Ibn al-Haytham left his impact on many scientific disciplines through his genius insight, and novel and original observations. Without doubt, he is considered as the pioneering father of modern optics.

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Good reporting of trials and observational studies: Related guidelines and initiatives

CONSORT (Consolidated Standards of Reporting Trials), is part of a broader push to produce reporting guidelines (RGs) for many different types of research. The main product of CONSORT is the CONSORT Statement <http://www.consort-statement.org/index>, which is an evidence-based, minimum set of recommendations for reporting RCTs. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. The CONSORT Statement comprises a 22-item checklist and a flow diagram, along with some brief descriptive text.

ASSERT

The ASSERT <http://www.assert-statement.org/> (A Standard for the Scientific and Ethical Review of Trials) initiative is a proposed standard for the review and monitoring of randomized clinical trials by research ethics committees. Among other items, its checklist incorporates certain elements of CONSORT, to ensure fulfillment of the requirements for scientific validity in the ethical conduct of clinical research.

EQUATOR

The EQUATOR <http://www.nks.nhs.uk/equator.asp> (Enhancing the QUAlity of Trials and Other Research) project aims to help fulfil the potential impact of reporting guidelines on the quality of research.

MOOSE

The MOOSE <http://www.consort-statement.org/index> (Meta-analysis of Observational Studies in Epidemiology) paper reports the outcome of a 1997 workshop to examine the reporting of meta-analyses of observational studies. It makes recommendations to aid authors, editors, reviewers and readers of observational research. (See CONSORT website)

QUOROM

The QUOROM (Quality Of Reporting Of Meta-analyses) conference resulted in the creation of the QUOROM Statement, which consists of a checklist and flow diagram. (See CONSORT website)

STARD

The STARD (Standards for Reporting of Diagnostic Accuracy) initiative aims to improve the accuracy and completeness of reporting of studies of diagnostic accuracy in order to allow readers to assess the potential for bias in a study and to evaluate the generalisability of its results. (See CONSORT website)

STROBE

STROBE <http://www.strobe-statement.org/> (STrengthening the Reporting of OBservational studies in Epidemiology) is an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and editors involved in the conduct and dissemination of observational studies.

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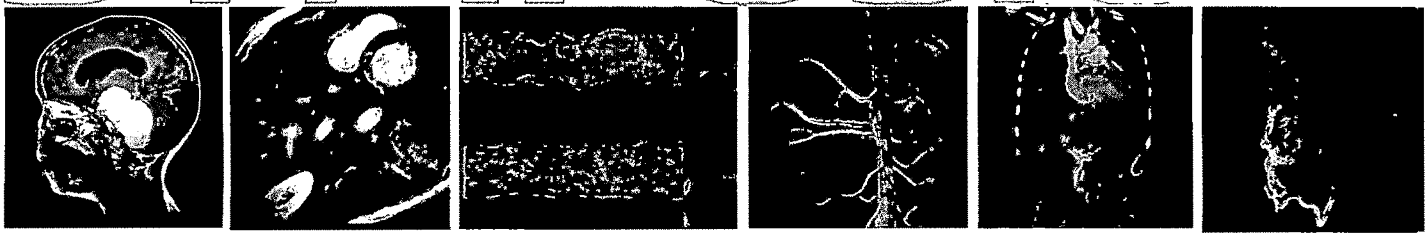

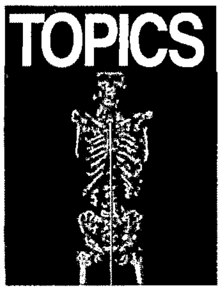

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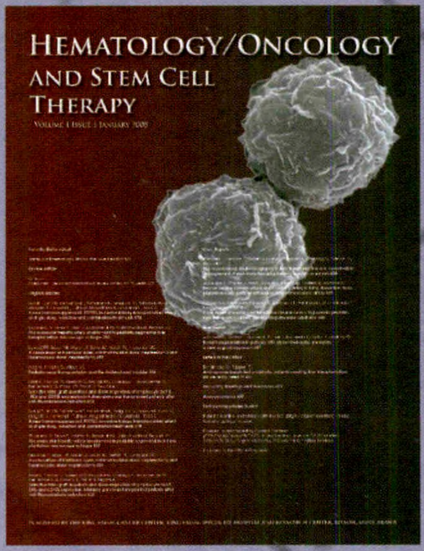

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السمات الباثولوجية السريرية للناميات الكبدية الشاذة في الكبد المستأصل إبان الاغتراس

المقدمة: قد تكون الناميات الكبدية الشاذة استطباباً مبدئياً لاغتراس الكبد. كما يمكن الكشف عن الأورام عرضياً في الكبد المستأصل. وقد قمنا باستقصاء السمات الباثولوجية السريرية للناميات الكبدية الشاذة في الأكباد المستأصلة إبان الاغتراس.

المرضى والطرق: تم تقييم جميع حالات الكبد المستأصل إبان الاغتراس ما بين العام ٢٠٠١م و٢٠٠٥م بالنسبة لوجود الناميات الشاذة وتم فحص السمات الباثولوجية السريرية.

النتائج: تم التعرف على ١٥ نامية شاذة (١٥,٣٪) في ٩٨ حالة اغتراس كبد. تراوحت أعمار المرضى بين ٥ و ٦٣ سنة (المتوسط، ٥٦ سنة). كان السبب الأولي للداء الكبدي هو فيروس التهاب الكبد (ج) في ١٢ حالة، وفيروس التهاب الكبد (ب) في حالة واحدة، وتليف خفي المنشأ في حالة واحدة، ولياف كبدي ولادي في حالة واحدة. كان ألفا – فيتوبروتين مرتفعاً في المصل بشكل ملحوظ في حالتين (٤٠٠، ١ وحدة في اللتر). (CA ١٩-٩ لم يكن مرتفعاً في أي من الحالات . شملت الأورام ورم سرطاني كبدي خلوي في ١٣ حالة، ورم سرطاني صفراوي في حالة وحدة، وورم سرطاني كبدي خلوي وورم أرومي كبدي في حالة واحدة. تراوح حجم الأورام من ٠,٥ إلى ٥ سم (المتوسط ١,٤سم) وكانت متعددة البؤر في ٥ حالات (٣٣٪). كان ألفا – فيتوبروتين النسجي موجوداً في الحالات التي تكون مستويات المصل بها مرتفعة فقط. توفي مريضان بسبب فشل الطعم أما باقي المرضى فهم أحياء ولا يوجد دليل على الداء في المتابعة بمتوسط ٢٠ شهراً.

الاستنتاج: تظهر الناميات الكبدية الشاذة في أكثر من ١٥٪ من حالات الكبد المغترس في مستشفانا. ويمكن الكشف عنها عرضياً وهي غير متعلقة بارتفاع مستويات مصل ألفا – فيتوبروتين عادة و (CA)١٩-٩ وهي عادة ما تكون متعددة البؤر ولكن صغيرة وتعتبر التوقعات المستقبلية بالشفاء جيدة لها. ارتفاع ألفا-فيتوبروتين في المصل نوعي لكنه ليس حساساً في الكشف عن الناميات الكبدية الشاذة.

الخلاصات العربية

انتشار مقاومة المتصورة المنجلية للصف الأول من العقاقير المضادة للملاريا ودرجة المقاومة: دراسة في الأنبوب من منطقة مستوطنة بالملاريا في اليمن.

المقدمة: كشفت دراسات غير منشورة لفعالية عقار مضاد للملاريا عن وجود مستويات منخفضة لمقاومة عقار "كلوروكين" في اليمن. وقد أجريت هذه الدراسة لتحديد الانتشار الحالي لمقاومة الدواء في المتصورة المنجلية للأدوية الرئيسية المضادة للملاريا في اليمن.

المرضى والطرق: تم استخدام البروتوكول القياسي لمنظمة الصحة العالمية (WHO) لاختيار المرضى وجمع عينات الدم وتقنية المزرعة وفحص شرائح الدم بعد المزرعة وتفسير النتائج. وقد تم استخدام الاختبار المجهري في الأنبوب (MARK III) لتقييم عنو معزولات المتصورة المنجلية.

النتائج: انطبقت القرائن لكثافة طفيلية الدم في ٢١٩ من المرضى المصابين بملاريا المتصورة المنجلية. وعند درجة تخفيف الدواء، والتي تشير إلى المقاومة، أظهرت نسبة ٤٧٪ من منقسمات المتصورة المنجلية المعزولة مقاومتها لعقار "كلوروكين"، ونسبة ٥,٢٪ مقاومتها لعقار "مفلوكين". بالإضافة، إلى أن قيم (EC٥٠) و (EC٩٥) في الدم، والتي ثبطت طور نمو المنقسمة، كانت أعلى من المستوى العلاجي الطبيعي لعقار "مفلوكين". ولم تحدث أي مقاومة ضد عقار "كينين" أو عقار "أرتيميسينين"، مع عدم حدوث نمو عند مستوى العزل لعقار "كينين" والكبح عند التركيزات المنخفضة لعقار "أرتيميسينين".

الاستنتاج: أكدت دراساتنا حدوث مقاومة المتصورة المنجلية لعقار "كلوروكين" وزيادة بطيئة في هذه المقاومة، ومن المحتمل أن هذه المقاومة ستتزايد بشكل أكثر وتنتشر على كل بؤر الملاريا في اليمن. وقد تم اكتشاف معدل منخفض لمقاومة المتصورة المنجلية لعقار "مفلوكين" في اليمن، والذي كان أقل من تلك التي تم الإبلاغ عنها في أفريقيا وجنوب شرق آسيا.

وفي النهاية، فإن المعزولات كانت حساسة للتركيزات المنخفضة لعقار "كينين" وعقار "أرتيميسينين".

الخلاصات العربية

كثافة العظم المعدنية لدى الأطفال المصابين بالذأب الحمامي المتعمم والالتهاب المفصلي الرثياني الشبابي

المقدمة: على الرغم من تزايد الاهتمام في استقلاب العظم لدى مرضى الاضطرابات الرثوية إلا أنه لا يتوفر سوى القليل من البيانات عن كثافة العظم المعدنية (كعم) لدى الأطفال المصابين باضطرابات رثوية وعلاقتها بالمتغيرات ذات العلاقة بالمرض. حددنا كعم لدى الأطفال الإيرانيين المصابين بذأب حمامي متعمم والتهاب مفصلي رثياني شبابي لتقييم العلاقة بين المتغيرات ذات العلاقة بالمرض وكعم.

المرضى والطرق: أجريت دراسة عرضية المقطع بين عامي ٢٠٠١ و٢٠٠٣ على عشرين مريضا (١٣ فتاة، و٧ فتيان) مصابين بالذأب الحمامي المتعمم (العدد ١٥) والالتهاب المفصلي الرثياني الشبابي (العدد ٥). متوسط أعمارهم ١٣,١٠ +٣,٢٩ سنة (مدى العمر ٦-١٧ سنة)، يراجعون في عيادة أمراض رثوية للأطفال، بالإضافة إلى مجموعة ضابطة من الأصحاء (العدد٢٠، تمت المطابقة مع كل مريض من حيث العمر والجنس). تم قياس كعم (غم/سم٢) لعنق عظم الفخذ (كعم-ع) والفقرات القطنية (كعم-ق) بطريقة قياس امتصاص الأشعة السينية مزدوجة الطاقة (DEXA). تم استقصاء الترابط بين كعم وبين الجرعة التراكمية للستيرويدات، والجرعة اليومية للستيرويدات، ومدة المرض، ونشاط المرض، والطول، والوزن، والعمر.

النتائج: كانت كعم لدى المرضى (كعم-ع=٠,٧٢+٠,١٥، كعم-ق=٠,٧٠+٠,١٩) أقل بدرجة مهمة مما هي لدى الأصحاء (كعم-ع=٠,٩٥+٠,١٧، كعم-ق= ٠,٩٨+٠,٢٠، (P<٠,٠٠١). كانت شدة انخفاض كعم أكثر وضوحا في الفقرات القطنية مما هي في عنق الفخذ (P=٠,٠٤) . لم يكن هناك ارتباط مستمر بين أي من المتغيرات وانخفاض كعم.

الاستنتاج: كانت كعم أقل بدرجة مهمة لدى المرضى بالمقارنة مع الأصحاء. كان انخفاض كعم أكثر وضوحا في الفقرات القطنية (العظم الإسفنجي). وعلى الرغم من أنه بدا أن للجرعة التراكمية للستيرويدات ومدة المرض تأثير على كعم إلا أنه لم يكن لأي منهما ترابط مستقل مع كعم.

الخلاصات العربية

منبئات انقطاع النفس النومي لدى الشخّيرين

المقدمة: الشخير مشكلة مألوفة تعرض صاحبها بدرجة كبيرة للإصابة بانقطاع النفس النومي. أجرينا دراسة على دور عوامل الخطورة للإصابة بانقطاع النفس النومي لدى الشخيرين وذلك بإجراء تخطيط متعدد أثناء النوم خلال ليلة كاملة.

المرضى والطرق: أعددنا استبياناً للمرضى الذين تمت إحالتهم لإجراء تصوير النوم المتعدد خلال الفترة من شهر إبريل ٢٠٠٢م وشهر مارس ٢٠٠٥م.

النتائج: تم التعرف على ١٩١ شخيّراً (٨٤٪) بعد ٢٢٧ تخطيط متعدد للنوم. كان متوسط أعمارهم ٤٨±٩,٨ عاماً، وتراوحت الأعمار بين ٢٣-٧٣ عاماً، نسبة ٧٨,٥ من الذكور. تم تحديد انقطاع النفس النومي بقيمة منسب اضطراب التنفس أكثر من ٥ مرات في الساعة وهو ما وجدناه في ١٢٦ مريضاً (٦٦٪). في الذكور أصيب ٧٢,٧٪ منهم بانقطاع النفس النومي مع متوسط اضطراب تنفسي ٤٣,٠±٢٦ مرة في الساعة مقابل ٣٩٪ من النساء أصبن بانقطاع النفس أثناء النوم مع متوسط اضطراب تنفسي ٢٦,٥±٢٧ مرة في الساعة (P<٠,٠٠١) ووفقاً لمقياس (Epworth) فكان متوسط انقطاع النفس أعلى في المجموعة الانسدادية (P<٠,٠٠١) وكان محيط العنق أكبر (P<٠,٠١) مع زيادة متوسط العمر (P<٠,٠٥) وزيادة في مناسب انقطاع النفس (P<٠,٠٠١) ولكن دونما اختناق (P= ٠,٠٩٦) إن الزيادة في منسب كتلة الجسم كانت مرتبطة فقط بالنساء (P<٠,٠٥) ولم تكن في الدراسة كلها (P=٠,٥٠٧) . أظهر التحليل متعدد التباين تبعاً لمقياس (Epworth) للنوم، للرجال، أن انقطاع النفس كان مرتبطاً بالنوم، مع ضبط عوامل البدانة، محيط العنق الكبير، العمر وتاريخ الاختناق.

الاستنتاج: كانت المنبئات الهامة لانقطاع النفس النومي هي إجراء التخطيط المتعدد للشخّيرين أثناء النوم، لفئة الرجال، الذين عانوا من انقطاع النفس باستخدام مقياس (Epworth) ولكن يجب أخذ العوامل الأخرى بعين الاعتبار لدى إحالة الشخيري لإجراء التخطيط المتعدد أثناء النوم. بالنسبة للرجال، فإن البدانة في دراستنا للمرضى لم تساهم في مخاطر الإصابة بانقطاع النفس الانسدادي النومي.

الخلاصات العربية

مقارنة بين التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب والتصوير القلبي بالرنين المغناطيسي لتقييم مقذوف البطين الأيسر الجزئي والأحجام

المقدمة: يمكن تحديد كل من مقذوف البطين الأيسر الجزئي وحجم نهاية الانبساط وحجم نهاية الانقباض بطرق غير باضعة بواسطة تخطيط صدى القلب ثنائي الأبعاد، والتصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، والتصوير القلبي بالرنين المغناطيسي. وقد وضعت هذه الدراسة بهدف تحليل التوافق بين قيم مقذوف البطين الأيسر الجزئي وحجم نهاية الانبساط وحجم نهاية الانقباض المستنتج من خلال تخطيط صدى القلب، والتصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، والتصوير القلبي بالرنين المغناطيسي .

المرضى والطرق: أجري تخطيط صدى القلب، والتصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، والتصوير القلبي بالرنين المغناطيسي على فئة مؤلفة من ١٢ مريضاً مشتبهاً في إصابتهم بمرض شرياني إكليلي. تم حساب قيم مقذوف البطين الأيسر الجزئي وحجم نهاية الانبساط وحجم نهاية الانقباض.

النتائج: بلغ متوسط مقذوف البطين الأيسر الجزئي المقاس بواسطة التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب، والتصوير القلبي بالرنين المغناطيسي ١٧,٨٪ ± ٥٥,٩، ١٦,٤٪ ± ٥٥,٧، ١٥,٧٪ ± ٥٦,٤ على التوالي. بلغ متوسط حجم نهاية الانبساط المقاس بواسطة التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب، والتصوير القلبي بالرنين المغناطيسي ٤٢,٤ ملم ± ١٠٩,٢، ٤٢,٢ ملم ± ١٢٧,٥، ٣٨,٠ ملم ± ٩١,١،على التوالي. بلغ متوسط حجم نهاية الانقباض المقاس بواسطة التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب، والتصوير القلبي بالرنين المغناطيسي ٢٤ ملم ± ٥٤,٢، ٣٧,٦ ملم ± ٥٩,٩، ٢٦,٩ ملم ± ٤١,٨ على التوالي. أظهرت نتائج تحليل التراجع الخطي ترابطاً جيداً جداً بين قيم مقذوف البطين الأيسر الجزئي وحجم نهاية الانقباض المقاس بواسطة التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب، والتصوير القلبي بالرنين المغناطيسي (r=٠,٩١، r=٠,٩٢، r=٠,٩٧ for LVEF & r=٠,٨٦، r=٠,٩١، r=٠,٩١ for ESV,P‹٠,٠١). تبين أيضاً وجود ترابطاً جيداً بين قيم مقذوف البطين الأيسر الجزئي وحجم نهاية الانبساط المقاس بواسطة التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب، والتصوير القلبي بالرنين المغناطيسي (r= ٠,٧١، r=٠,٦٨، r=٠,٧٣,P‹٠,٠١). كان التوافق بين هذه التقنيات في قيم مقذوف البطين الأيسر الجزئي كان جيداً أيضاً ولكن ليس في قيم البطين الأيسر وفقاً لمخطط بلاند- الترمان.

الاستنتاج: أظهرت الدراسة تربطاً عاماً جيداً بين قيم المقذوف الجزئي للبطين الأيسر وحجم نهاية الانبساط وحجم نهاية الانقباض المستقاة من التصوير المقطعي بالحاسوب بانبعاث الفوتون الفردي المواقت، وتخطيط صدى القلب، والتصوير القلبي بالرنين المغناطيسي. يمكن استخدام نتيجة المقذوف الجزئي للبطين الأيسر المستقاة من أي من الفحوص الثلاثة تبادلياً، مع الحذر عند مقارنة القيم الخاصة بأحجام البطين الأيسر.

دور فيتامين هـ في الوقاية من السرطان: تحليل شامل للدراسات المضبوطة العشوائية

المقدمة: أجرينا تحليلا شاملا للدراسات المضبوطة العشوائية لتقييم دور فيتامين هـ في الوقاية من السرطان لدى البالغين.

الطرق: شمل هذا التحليل الدراسات المضبوطة العشوائية التي تمت فيها مقارنة نتائج تناول فيتامين هـ، كمكمل غذائي لوحده أو مع مكملات أخرى، مع مجموعة ضابطة. كانت المآلات الرئيسية هي إجمالي الوفاة، الوفاة بالسرطان، إجمالي الإصابة بالسرطان، الإصابة بسرطانات الرئة والمعدة والمرئ والبنكرياس والبروستاتة والثدي والدرقية. تمت مراجعة جميع الدراسات التي تم التعرف عليها من قبل مراجعين اثنين بصفة مستقلة لتحديد ما إذا كانت الدراسة سيتم إدراجها في التحليل أم لا. تم تقييم نوعية جميع الدراسات المشمولة بالتحليل بصفة مستقلة من قبل مراجعين اثنين.

النتائج: استوفت ١٢ دراسة (ضمت ما مجموعه ١٦٧٠٢٥ مشاركا) معايير الإدراج. لم تكن هناك فروق مهمة إحصائيا من حيث إجمالي الوفاة (الخطورة النسبية ٠,٩٩، مدى الثقة-٩٥٪ ٠,٩٦-١,٠٣)، والإصابة بالسرطان (نسبة الاحتمالية ٠,٩٦، م ث-٩٥٪ ٠,٩٢-١,٠١)، والوفاة بالسرطان (نسبة الأرجحية ١,٠٠، م ث-٩٥٪ ٠,٩٦-١,٠٣) بين المجموعات المختلفة من المرضى المشمولين في هذا التحليل. صاحب فيتامين هـ انخفاض مهم في الإصابة بسرطان البروستاتة (الخطورة النسبية ٠,٨٥، م ث-٩٥٪ ٠,٧٣-٠,٩٦ ، عدد من احتاج للعلاج ٥٠٠) ولكنه لم يخفض الإصابة بأي نوع آخر من السرطان.

الاستنتاج: لم يصاحب تناول فيتامين هـ كمكمل غذائي انخفاض في إجمالي الوفاة أو الإصابة بالسرطان أو الوفاة بالسرطان، ولكن صاحبه انخفاض مهم إحصائيا في الإصابة بسرطان البروستاتة. لذا، يمكن استعمال فيتامين هـ للوقاية من سرطان البروستاتة لدى الرجال الذين يكون احتمال إصابتهم به مرتفعا.

المدونات الطبية السعودية

السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصّصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول مكتب المطبوعات (ر.إ ٣٦).

سعر الاشتراك ١٠٠ ريال في السنة للأفراد داخل المملكة و٢٠٠ ريال في السنة للأفراد خارج المملكة و٥٠٠ ريال في السنة للمؤسسات. يمكن فتح اشتراك مجاني للأفراد و المؤسسات في الدول النامية.

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SYMPOSIA

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Pediatric in Saudi Arabia in 21st Century
13-14 May 2008/08-09 Jumada Al Awal 1429
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A New Prospective in Gynecology & Women's Health Care
03-04 June 2008/29-30 Jumada Al Awal 1429

Frontiers in Surgical Pathology Symposium
28-29 October 2008/28-29 Shawwal 1429

International Symposium on Infections in Immunocompromised Host
18-19 November 2008/20-21 Dhu Al Qeada 1429
(Workshop by Dept.: 20 November 2008/22 Dhu Al Qaeda 1429)

Advances in Endoscopic Sinus Surgery
02-03 December 2008/04-05 Dhu Al Hijjah 1429

COURSES

Theory & Practice of Gas and Liquid Chromatography in Pharmaceutical & Biomedical Applications
15-18 March 2008/07-10 Rabia Al Awal 1429

Orthopedic MRI Course
24-26 March 2008/16-18 Rabia Al Awal 1429

Internal Medicine Saudi Board Review Course
11-15 October 2008/11-15 Shawwal 1429

Project Materials in Internal Medicine Course
16 October 2008/16 Shawwal 1429

Saudi Board Clinical Preparatory Review Course
19-20 November 2008/21-22 Dhu Al Qeada 1429

WORKSHOPS

Brain Gliomas Workshop: Hope for the Future
12-13 February 2008/05-06 Safar 1429

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19-20 February 2008/12-13 Safar 1429

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11-12 March 2008/03-04 Rabia Al Awal 1429

Reconstructive and Aesthetic Breast Surgery Workshop
08-09 April 2008/02-03 Rabia Al Thani 1429

8th Annual Neonatology Meeting
14-16 April 2008/08-10 Rabia Al Thani 1429

Genetic Counselling and Preventative Screening Programs in the Kingdom of Saudi Arabia: Now and Future
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04-05 November 2008/06-07 Dhu Al Qeada 1429

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King Faisal Cancer Centre Academic & Research Day
08 May 2008/03 Jumada Al Awal 1429

8th Annual Surgical Research & Residents' Day
27 November 2008/29 Dhu Al Qeada 1429

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